THE EFFECT OF "FUSAFUNGINE" ON THE INCIDENCE OF UPPER RESPIRATORY TRACT SYMPTOMS IN ULTRADISTANCE RUNNERS

In partial fulfillment of the MPhil.(Sports Medicine) degree

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Chapter 1

Introduction and scope of the thesis

Upper respiratory tract infections (URTI's) are of particular importance to ultradistance runners. Even a minor illness can limit training and may impair sports performance. Many athletes believe that regular strenuous exercise improves their resistance to infection and there are anecdotal reports that athletes have fewer upper respiratory tract infections (Brenner et al, 1994).

However, in runners it has been found that the risk of developing symptoms of upper respiratory tract infections within two weeks after an ultramarathon (56km) event is double compared to sedentary controls (Peters et al, 1983). It also been shown that the risk of an "infectious episode" was fivefold higher in runners one week after a marathon race than in runners who trained but did not compete in the race (Nieman et al, 1990). There also seems to be a significant association between the development of upper respiratory tract symptoms and high weekly training distance (Heath et al, 1991; Nieman et al, 1990; Peters et al, 1983; Peters et al, 1993). Moreover, faster runners reported more symptoms, indicating a possible relationship between exercise intensity and the development of upper respiratory tract symptoms (Brenner et al, 1994; Peters et al, 1990).

The precise mechanism by which high intensity, prolonged exercise increases the susceptibility to symptoms of upper respiratory tract infections remains obscure.

Studies investigating the relationship between exercise and immune function have demonstrated a wide variety of changes in immune function in response to both acute bouts of exercise as well as prolonged regular exercise training (Berk et al, 1990; Kappel et al, 1991; Mackinnon et al, 1987; Mackinnon et al, 1993; Nieman et al, 1989; Nieman et al, 1995; Nieman et al, 1993; Nieman et al, 1991; Nieman et al, 1990; Nieman et al, 1989; Pedersen et al, 1989; Pedersen et al, 1988; Pedersen et al, 1994). In general, detrimental changes to the immune system can be documented in response to very high intensity exercise, or excessively prolonged exercise bouts (Mackinnon et al, 1987; Mackinnon et al, 1993; Nieman et al, 1992; Nieman et al, 1989; Weight et al, 1991).

Food intake may also play a role and poor nutrition could result in an impaired immune response (Shephard et al, 1993). Specifically, deficiencies of anti-oxidant vitamins, as well as some amino acids, trace elements and essential fatty acids have been implicated in impaired host defence (Daly et al, 1990; Peters et al, 1993; Peters et al, 1996).

One of the major limitations of most of the epidemiological studies investigating the relationship between symptoms of upper respiratory tract infections and exercise is that they have relied on self reported symptoms. The true measure of the outcome (URTI) is difficult to ascertain without an adequate clinical examination and laboratory documentation of the infection. Symptoms reported by athletes may not necessarily be accompanied by infection and may simply be a local inflammatory

response to mechanical irritation of the upper respiratory tract (Brenner et al, 1994; Peters et al, 1983; Shephard et al 1993). This is based on the observation that most symptoms occur within two to three days and are localized to the respiratory tract without systemic symptoms (Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996). However, this hypothesis has not been tested in a well conducted clinical study.

Fusafungine is an antibiotic of fungal origin with a potent local anti-inflammatory action (German-Fattal, 1995; German-Fattal, 1996). It is administered locally to the nasal and pharyngeal mucosa by spray. It can be hypothesised that the anti-inflammatory action of fusafungine may decrease the development of mucosal inflammation in such a manner that the incidence of symptoms of upper respiratory tract infection may be reduced if it is administered before, during and after completion of an ultramarathon. Furthermore, fusafungine could also reduce the risk of secondary bacterial infection. The potential value of fusafungine in reducing the symptoms of upper respiratory tract infections or the development of bacterial upper respiratory infection is the focus of this thesis.

Chapter 2

Literature review: URTI in endurance runners

2.1. Upper respiratory infections

2.1.a. Definition

Upper respiratory tract infections consist of a number of acute illnesses that occur in the upper portion of the respiratory tract (Heath et al, 1992). The classification of respiratory tract infections as "upper" (affecting the nose and throat) or "lower" (affecting the bronchiolar pulmonary tissue) is an over-simplification as most pathogens infect both upper and lower respiratory tracts (Timbury, 1986). Infants and children have the highest incidence of upper respiratory tract infection with four to eight episodes per year (Heath et al, 1992). In general, the incidence decreases with age and adults usually acquire between two and five upper respiratory tract infections per year (Heath et al, 1992).

2.1.b. Aetiology

The aetiology of upper respiratory tract infections is viral in more than 90% of cases. Almost 200 different viruses have been implicated, but *Rhinovirus* or *Coronavirus* are the most common pathogens (Heath et al, 1992). Other viruses that have been implicated include the *Parainfluenza, Respiratory syncytial, Influenza, Adeno, Coxsackie and Echo viruses* (Table 2.1).

The *Beta-haemolytic streptococcus* is the predominant bacterial cause of upper respiratory tract symptoms. *Haemophilus influenzae* causes acute epiglotitis, otitis media and occasionally pneumonia. *Streptococcus pneumoniae* tends to affect the lower respiratory tract predominantly. Other bacterial causes of respiratory tract infection include *Mycoplasma pneumoniae, Staphylococcus aureus* and *anaerobes* (Robinson, 1990).

Table 2.1: Viruses associated with the common cold.

VIRUS	PREDOMINANT SEASONS
Most common	
Rhinoviruses	Autumn, mid-spring to summer
Coronaviruses	Winter
Common	
Parainfluenza viruses	Autumn, spring
Respiratory syncytial viruses	Winter to early spring
Influenza viruses	Winter
Less common	
Adenoviruses	All seasons
Enteroviruses	Summer, autumn
Reoviruses	All seasons

Adapted from Hall & McBride, 1989.

2.1.c. Pathophysiology

Transmission of the viruses that cause upper respiratory tract infection usually takes place by close contact with an infected person (Heath et al, 1992). Viral particles may be suspended in droplets caused by a cough or sneeze and transmitted directly to the upper respiratory passages or conjuctiva of a susceptible individual (Heath et al, 1992). The virus may also be spread from contaminated surfaces by hand to the mucous membranes (self-innoculation) as well as direct transmission from the hand of an infected person to the hand of another who may then touch their nasal or conjunctival mucosa and acquire an infection (Heath et al, 1992).

2.1.d. Clinical features

The most common upper respiratory tract symptom complex is that of acute coryza (the "common cold"). Typical symptoms include nasal catarrh, cough and sore throat with minimal fever and little or no systemic complaints. Other less common manifestations of upper respiratory tract infections include, pharyngitis, croup, bacterial tracheitis or epiglotitis (Heath et al, 1992).

2.1.e. Diagnosis

The diagnosis of an upper respiratory tract infection is made on a typical history, clinical examination and isolation of the infective agent. Serology is of limited value due to the large number of viruses (and their many serological types) that may cause upper respiratory tract infection (Timbury, 1986). Furthermore, the history of typical symptoms is confounded in athletes by other factors. Obligatory mouth

breathing that occurs during prolonged exercise may cause drying of the respiratory mucosa and slowing of ciliary action (Rylander, 1968). Exposure to cold or atmospheric pollutants may also cause irritation of the airways. In addition, symptoms may arise from a secondary infection or bronchospasm (Brenner et al, 1994). The true diagnosis of an upper respiratory tract infection should be based on clinical findings and laboratory confirmation of infection (Heath et al, 1992).

2.1.f. Treatment

In general, because upper respiratory tract infections are caused in the majority of cases by viruses and are therefore self-limiting, only symptomatic treatment is required (Timbury, 1986). Adequate fluid intake, rest and treatment with analgesics and possibly decongestants is all that is required in the majority of cases (Brenner et al, 1994; Timbury, 1986). Any secondary bacterial infection should be treated with an appropriate antibiotic. The importance of infection in athletes however, is more significant with the potential for developing a myocarditis or sudden death in those who continue to exercise while infected with a virus. Athletes should therefore be advised to follow a suggested "neck check" (Eichner, 1993) when deciding to exercise while infected. If all the symptoms are " above the neck" (runny or stuffy nose, scratchy throat), the athlete could begin their exercise routine at below normal intensity for ten minutes. If the activity made them feel worse, they should stop exercising, but if they feel better, they can continue with training. However, if any symptoms were "below the neck" (muscle aches, cough, vomiting, diarrhoea or fever) training should be discontinued (Eichner, 1993). Exercise should only be

started at least fourteen days after the cessation of these symptoms (Heath et al, 1992).

2.1.g. Prevention

The most effective way to prevent infection is to minimise exposure to pathogens (Shephard et al, 1993). Athletes should avoid contact with infected individuals (especially children) and any team members who have symptoms should be isolated from their peers. Since viruses are often transmitted by hand contact, the hands should be washed regularly and any rubbing of the eyes or of the nose should be avoided (Shephard et al, 1993).

For those athletes engaged in heavy training further preventative measures include spacing vigorous workouts and race events as far apart as possible, eating a well balanced diet, keeping life stresses to a minimum, avoiding over-training and chronic fatigue and obtaining adequate sleep (Heath et al, 1992). Vitamin supplementation (especially vitamin C) may also be beneficial (Peters et al, 1993).

Lastly, the innoculation of viruses endemic to the area where an athlete will compete may be useful (Shephard et al, 1993). Immunoglobulin that is injected intra-muscularly may reduce the incidence, duration and severity of upper respiratory tract illness in athletes (Nieman et al, 1991).

2.2. The effect of exercise on the immune system

A large number of scientific studies have been performed to determine the effects of exercise on the various components of the immune system. In general, detrimental changes to the immune system can be documented in response to very high intensity exercise or excessively prolonged exercise bouts.

A wide variety of changes in immune status have been documented in association with acute exercise. However, most of these are transient and reverse within hours of the exercise bout (Simon, 1987). Changes that occur include alterations in the ratio of T-helper to suppressor cells, serum immunoglobulin levels, and the proliferative response of the peripheral blood mononuclear cells to standard mitogens.

Immediately after a bout of high intensity exercise a leukocytosis (Nieman et al, 1992; Weight et al, 1991) can be demonstrated. It has been shown that both neutrophils and lymphocytes increase after exercise representing approximately 60% and 30% of the leukocytes respectively (Nieman et al, 1992). However, after approximately an hour, the lymphocyte count decreased to 36% below pre-test levels. The immediate post exercise increase in lymphocytes was due to a large increase in natural killer cells and a smaller increase in cytotoxic/ suppressor T cells. A sharp decrease in total T cells and a moderate decrease in NK cells was responsible for the recovery lymphopenia. The lymphocyte count remained low for 36 hours. These increases in the leukocyte count appear to be as a result of

exercise induced increases in serum adrenaline and cortisol concentrations. Adrenaline is known to increase the number of leukocytes substantially (Nieman, 1994). In contrast, increased cortisol is known to induce neutrophilia and cause a lymphocytopenia (Nieman, 1994). Immediately after exercise, adrenaline serum concentrations decrease to pre-exercise serum concentrations while serum cortisol concentrations remain elevated resulting in a reduction in the number of leukocytes.

One component of the immune defences that has shown a more prolonged effect from exercise is the natural killer (NK) population (Shephard et al, 1993).The NK cells are a heterogeneous but important subset of lymphocytes capable of destroying cells that are infected with viruses and other micro-organisms without prior exposure. As little as one hour of exercise at 60% $VO_{2\ max}$ has been shown to reduce NK activity to 50% of normal, with recovery being incomplete two hours later (Shephard et al, 1993). More prolonged and intensive exercise, such as a marathon run, has left the lytic activity of NK cells depressed the following day (Shephard et al, 1993). Various prostaglandins are capable of inhibiting the cytotoxic activity of NK cells. It has been demonstrated that the post exercise suppression of NK cells may be related to increased serum concentrations of prostaglandins that are released from monocytes (Kappel et al, 1991). Indomethacin abolished this suppressed NK cell activity in vitro (Kappel et al, 1991). It has been shown that there is a 59% increase in serum cortisol concentrations in well trained marathoners who ran their fastest marathon pace on a treadmill for three hours (Berk et al, 1990; Nieman et al, 1989). This increase in serum cortisol concentrations correlated

inversely with a 25 - 46% decrease in NK cell activity at 1.5 hours after recovery which persisted for nearly six hours although serum cortisol concentration returned to normal at 1.5 hours.

The serum concentrations of C3 and C4, but not IgG, IgA or IgM, are decreased during rest, graded submaximal exercise, and during recovery in marathon runners compared with sedentary controls (Nieman et al, 1989). However, secretory IgA, the principle immunoglobulin in local secretions of the mucosal surfaces of the upper airways, has been shown to be decreased after intense endurance exercise (Mackinnon et al, 1987; Tomasi et al, 1982) and brief supramaximal interval exercise (Mackinnon et al, 1993). It has been suggested that low secretory IgA levels may result from depletion of nasal fluid and/or malfunction of the mucosal plasma cells due to a decrease in the temperature of the mucous membranes. This might lead to an increased susceptibility to viral and bacterial infections, especially in the interval immediately following strenuous exercise (Tomasi et al, 1982). Besides the fall in secretory IgA, there may also be changes in the physical properties of the protective mucous layer, impaired mucocilliary clearance and macrophage function during exercise (MacNab et al, 1981). Changes in the factors protecting the mucosal surfaces such as lysozymes and interferon may also increase the risk of upper respiratory tract infection in response to exercise (MacNab et al, 1981).

A further factor that may account for the increased risk of upper respiratory tract infections in athletes, is the involvement of the immune system in the tissue repair process that occurs following strenuous exercise. It has been well established that both high intensity acute exercise bouts and prolonged exercise are associated with muscle cell damage, local inflammation and the sequence of host defence reactions known as the acute phase response (Evans et al, 1991). It is possible that host protection from infection may be compromised during the time the immune system is involved in tissue repair following high intensity exercise, but this has yet to be measured objectively (Nieman, 1994).

Food intake and poor nutrition may also play a role in impairing the immune response (Shephard et al, 1993). In some instances the athlete's diet may fail to meet the demands imposed by a high level of energy expenditure and repeated depletion of glycogen stores. Deficiencies of many amino acids, trace elements, essential fatty acids and vitamins have been associated with impaired host defence against infection (Daly et al, 1990; Peters et al, 1993; Peters et al, 1996).

Finally, psychological factors may also play an important role in the relationship between exercise and upper respiratory infections. An intensive exercise program is a form of physiological stress (Heath et al, 1992) and the combination may compromise the ability of the immune system to protect the host. Mental stress alone has been related to a wide variety of negative changes in immune system function (Jemmott et al, 1984).

Bereavement, major depression, schizophrenia, marital discord and other forms of mental stress have all been associated with suppression of immune function (Jemmott et al, 1984).

In conclusion, the effect of combined psychological and physiological stress from high intensity endurance exercise, especially during times of competition may lead to suppression or down-regulation of the immune system (Heath et al, 1992).

Based on the observed immunological changes following exercise, an "open window" hypothesis has been proposed to account for the increased risk of respiratory tract infection following intensive exercise (Pedersen et al, 1994). During moderate as well as acute exercise, the immune system is enhanced (Figure 2.1), but in response to high intensity exercise immunosuppression occurs (Figure 2.2). It is during this time that the athlete is at risk for infection by microbial agents, especially viruses. However, in those athletes who perform regular moderate exercise, the immune system will be enhanced and this may protect from illness.

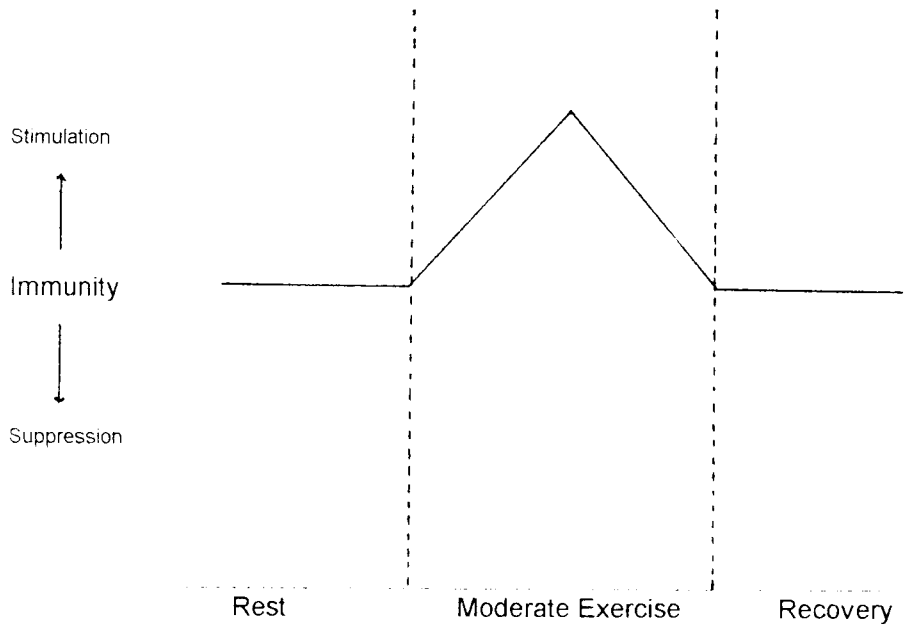

Figure 2.1: Immune system response to acute moderate intensity exercise.

Adapted from Pedersen and Ullum, 1994.

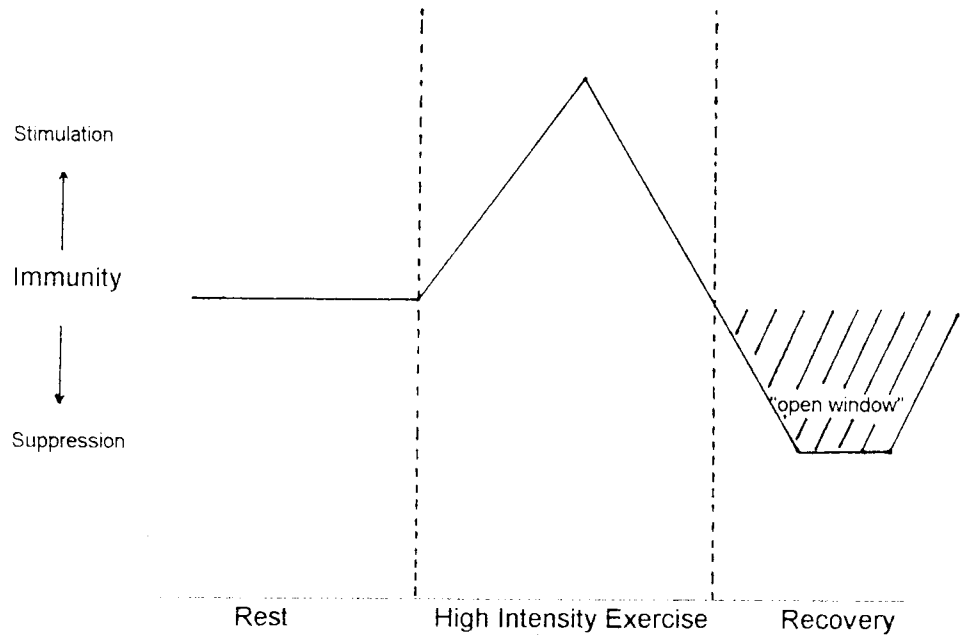

Figure 2.2: "The open window" hypothesis. Immune system response to acute high intensity exercise.

Adapted from Pedersen and Ullum, 1994.

2.3. Epidemiology and risk factors of URTI in endurance runners

A number of scientific studies have shown that endurance athletes are at increased risk for developing symptoms of upper respiratory tract infection (Nieman et al, 1990; Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996). This is especially so at times of intense training and during the two week post-race period.

The first investigators to demonstrate this increased risk for the development of upper respiratory tract symptoms after an ultradistance event were Peters and Bateman (Peters et al, 1983) in their study at the 1982 Two Oceans ultramarathon (56km). One hundred and fifty race finishers were compared with age-matched non-running controls. The runners completed a questionnaire on the day before the race and both the runners and controls were questioned regarding the development of upper respiratory tract symptoms during the fourteen day post race period. Nine athletes failed to complete the race and were excluded from the trial. Of the runners, 33.3% reported symptoms of upper respiratory tract infections during the two week post-race period compared to 15.3% of the control group. The most prevalent symptom after the race was sore throat (41%), followed by nasal symptoms (36%), including a runny nose and/or sneezing. A cough was less common (19%) and only three subjects developed fever in conjunction with one or more of the upper respiratory tract symptoms (Table 2.2). In this study, 80% of the affected runners developed symptoms which lasted for more than three days, and

the investigators suggested that an infective process was responsible for the symptoms.

Table 2.2: The nature and duration of upper respiratory tract symptoms after an ultramarathon run at sea level.

	Duration of symptoms (days)					
Symptoms	**< 1 day**	**1 - 3 days**	**4 - 7 days**	**> 7 days**	**Total**	**% Total**
Sore throat	6	2	12	12	32	41
Nasal symptoms	1	5	8	14	28	36
Cough	1	0	5	9	15	19
Fever with upper respiratory tract symptoms	0	0	1	2	3	4
Total	8	7	26	37	78	100

Adapted from Peters et al, 1993.

The incidence of upper respiratory tract symptoms was the highest in the fastest runners ($p < 0.01$) with 47% of runners who finished in less than four hours reporting symptoms (Figure 2.3).

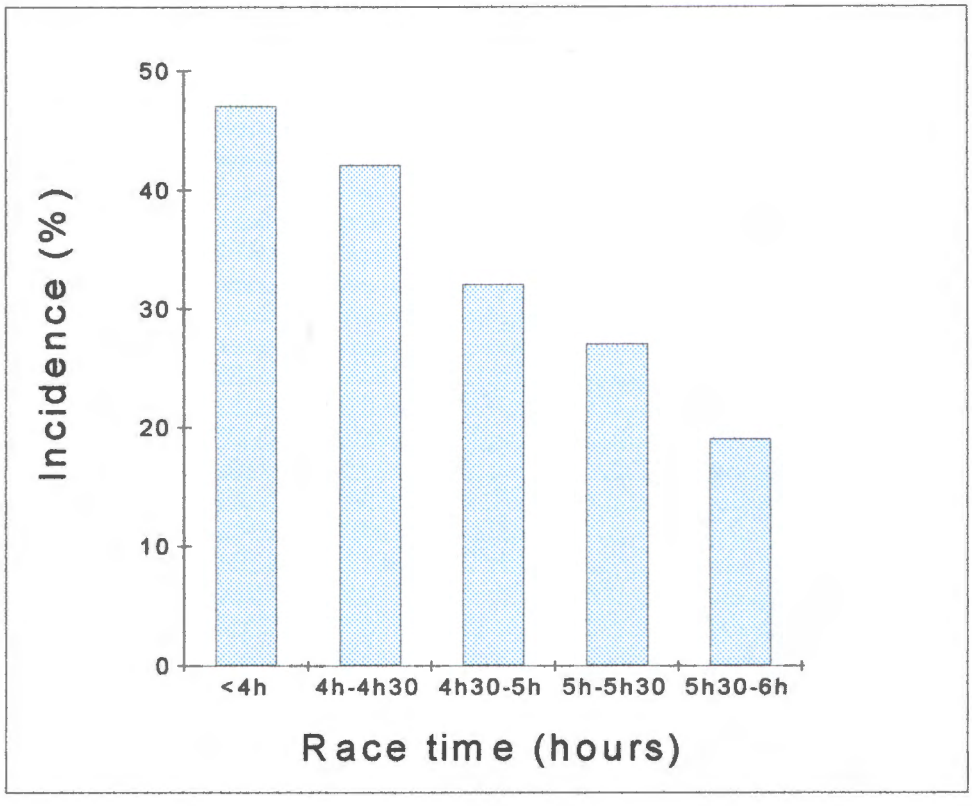

Figure 2.3: The incidence of upper respiratory tract symptoms according to time taken to complete the race (n = 141).

Adapted from Peters et al, 1983.

There was significant association ($p < 0.01$) between symptoms and high weekly training distance. Athletes who were training more than sixty five kilometres per week were at greater risk of developing upper respiratory tract symptoms (Table 2.3).

Table 2.3: Upper respiratory tract symptoms in relation to training distance per week before the race (n = 141).

	Symptomatic runners	Asymptomatic runners
< 65km/wk	9	36
> 65km/wk	38	56

Adapted from Peters and Bateman, 1983.

The investigators suggested that the higher incidence of upper respiratory tract symptoms in the immediate post-race period can be attributed to one or both of the following: (1) the impairment of general host resistance to infection resulting from the extreme stress and fatigue of running an ultramarathon or (2) the physical affects of cold and dry air on local mucosal defences. The investigators also point out that local trauma may occur to the mucous membranes as a result of mouth breathing. The increased minute ventilation required during submaximal exercise may be responsible for or contribute to this trauma. In an ultramarathon, this may continue for four to five hours or longer.Based on these assumptions, Peters (Peters, 1990) repeated the study at another 56 kilometre ultramarathon. This marathon however, took place at altitude (± 1600 metres above sea level) and a relative humidity of 52%. This is lower than the relative humidity at sea level, (79%). It was hypothesised that the amount of damage to the mucous membranes should

be greater at altitude due to drier inhaled air and the increased ventilation at a given running speed.

The methodology was the same as in the previous study. Thirty one (28.7%) of the one hundred and eight subjects who completed the race reported non-allergy related upper respiratory tract symptoms during the two weeks following the race as compared to fourteen (12%) among the control group. This was a significantly higher incidence ($p < 0.005$). The most prevalent symptoms after the race were blocked or runny nose (57%), followed by a sore throat (30%). Thirty nine percent of the symptoms lasted for more than seven days and only two runners reported fever accompanying the symptoms (Table 2.4).

Table 2.4: The nature and duration of respiratory tract symptoms after an ultradistance race at altitude (n = 46).

	Duration of symptoms (days)					
Symptoms	**< 1 day**	**1 - 3 days**	**4 - 7 days**	**> 7 days**	**Total**	**% Total**
Nasal	4	9	2	11	26	57
Sore throat	0	9	2	3	14	30
Cough	0	1	1	2	4	9
Fever	0	0	0	2	2	4
Total	4	19	5	18	46	100

Adapted from Peters, 1990.

This study confirmed their previous findings of a significantly higher incidence of upper respiratory tract symptoms amongst runners compared to matched sedentary

controls following participation in an ultradistance marathon event. However, in this study the exposure to moderate altitude with the concomitant increase in pulmonary ventilation and drier air did not result in an increased incidence of upper respiratory tract symptoms compared to runners at sea level (Figure 2.4). These results appear to indicate that altitude and relative humidity do not influence the incidence of upper respiratory tract symptoms after ultradistance running.

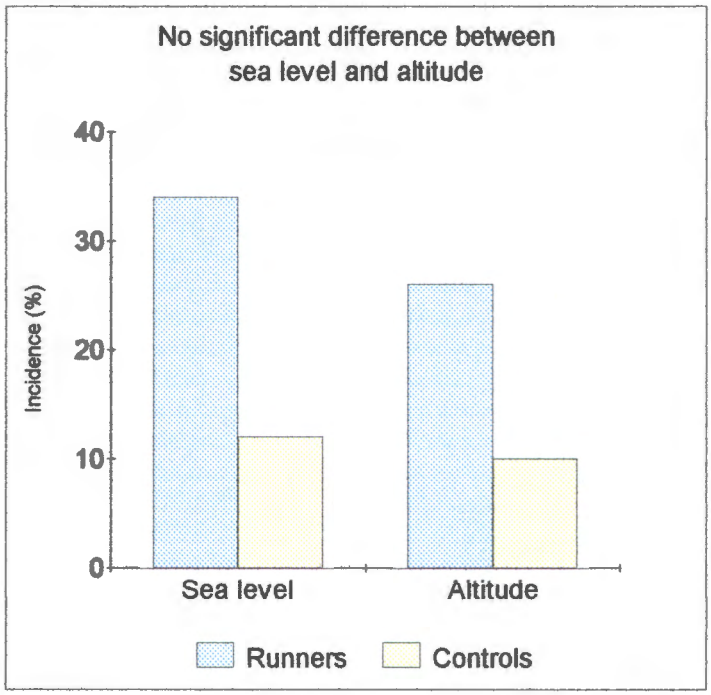

Figure 2.4: A comparison of the incidence of URT symptoms amongst runners and controls at moderate altitude (1800m) and sea level.

Adapted from Peters, 1990.

In this second study, there was also a higher incidence of symptoms (± 32%) amongst the faster athletes. Furthemore, athletes who took longer than six hours to complete the race also showed increased incidence of upper respiratory tract symptoms. It appears that prolonged physiological stress may also decrease host resistance and predispose to the development of symptoms. This study also showed that the less trained runners had the highest incidence of symptoms.

Vitamin C is an anti-oxidant that may reduce the risk of developing respiratory tract infection (Anderson et al, 1972; Baird et al, 1979; Bucca et al, 1989; Chalmers, 1975; Hodges et al, 1980; Mink et al, 1988; Schwartz et al, 1990). Exercise increases the production of oxygen free radicals which may depress immune function by inhibiting leukocyte chemotaxis (Kanter et al, 1988; Packer, 1986). It is therefore possible that anti-oxidants, including Vitamin C, may be required in high doses in athletes to oppose the effect of these free radicals (Anderson, 1984; Bendich et al, 1986). A study (Peters et al, 1993) was conducted to determine whether daily supplementation with 600mg Vitamin C would reduce the incidence of upper respiratory tract infections after an ultramarathon. Ninety two runners who entered the 1990 Comrades Marathon (90km) nominated a control non-running subject of similar age. A double-blind placebo controlled study was conducted in which half the runners and controls were required to take 600mg of Vitamin C daily for twenty one days prior to the marathon while the remaining runners and controls ingested placebo. Each subject completed a questionnaire prior to the race documenting demographic data regarding their running history. The runners were

asked to detail all forms of vitamin or mineral supplementation and a 24 hour dietary recall was used to establish their daily dietary intake. Two weeks after the race the subjects were questioned by telephonic interview regarding the development and duration of symptoms (nasal, sore throat, cough and fever) of upper respiratory tract infection. Total Vitamin C intake was calculated in each subject and in those runners who took supplements of 600mg Vitamin C, their total daily Vitamin C intake was in excess of 1g. The Vitamin C supplemented groups of runners and the age matched control subjects had significantly higher daily Vitamin C intakes (1139g $\pm$ 452) when compared with runners (494g $\pm$ 390) and their controls (280g $\pm$ 202) who received placebos ($p < 0.01$).

During the two week post-race period, significantly fewer subjects (33% vs. 68%; $p < 0.01$) who were supplemented with Vitamin C reported symptoms of upper respiratory tract infection (Figure 2.5).

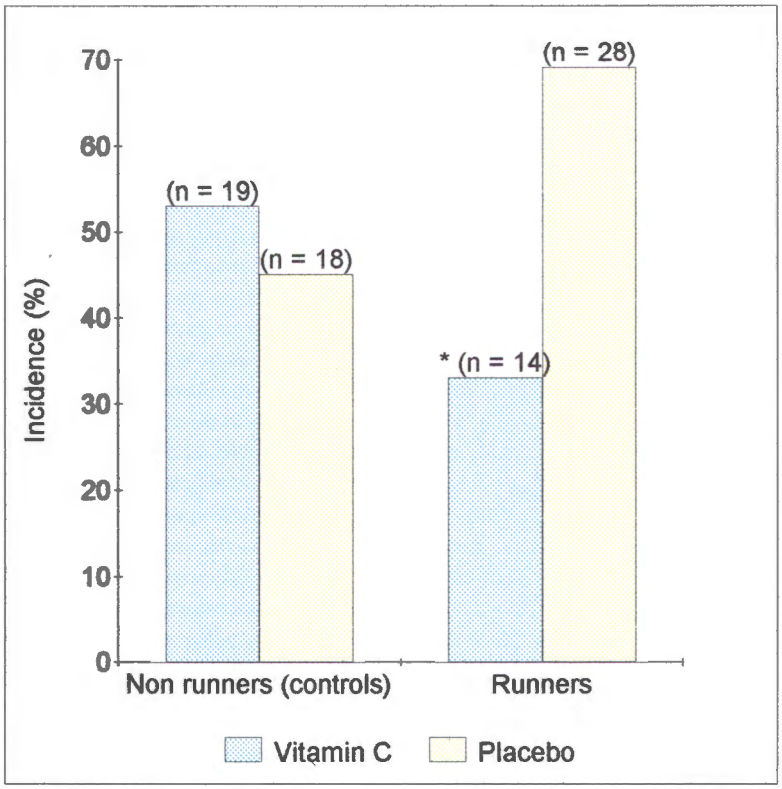

Figure 2.5: The incidence of symptoms of URT infection in runners and non runners (controls) receiving either 600mg Vitamin C or a placebo. Significant difference (* $p < 0.05$).

Adapted from Peters et al, 1993.

In this study, the incidence of symptoms was greatest in those who fell into a high training status group (Figure 2.6). The training status ratio of each runner was calculated using the following formula:

$$\frac{\textit{Weekly training distance (km) x no. of weeks spent in training}}{\textit{average speed at which those kilometres were covered}}$$

Runners who reported a ratio of > 450 constituted the high-training status category, whereas those with a ratio < 300 were classified in the low-training status catagory

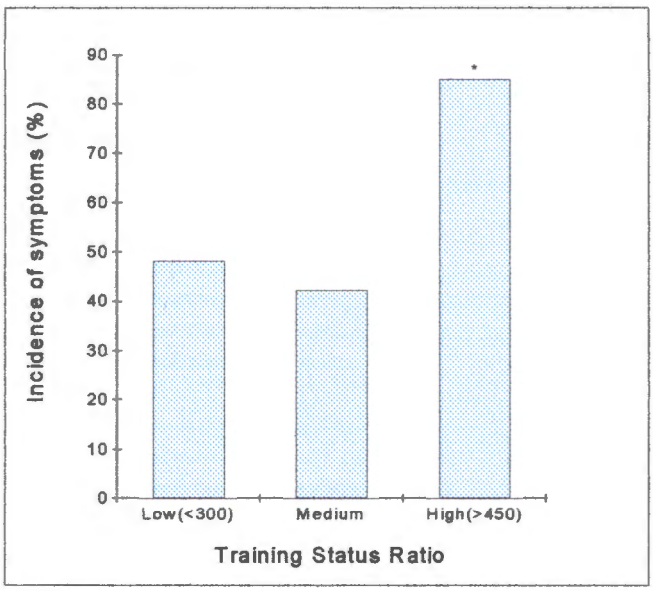

Figure 2.6: The incidence of post-race URT symptoms in low, medium and high training status groups (n = 77). Significantly different (* p < 0.01) from percentage symptomatic in the low and medium training status groups.

Adapted from Peters et al, 1993.

There was however no correlation between the time in which the race was completed and the reported incidence of symptoms. In a subsequent study at the 1993 Comrades Marathon (Peters et al 1996), compared the efficacy of supplementation with combinations of Vitamin E, Vitamin C and Beta Carotene versus Vitamin C alone in reducing symptoms of post-race upper respiratory tract infection.

A double-blind, placebo controlled study design was used in which runners (n = 178) and sedentary matched controls (n = 162) were randomly divided into groups receiving 500mg Vitamin C (n = 86), 500mg Vitamin C and 400iu Vitamin E (n = 90) or 300mg Vitamin C, 300iu Vitamin E and 18mg Beta Carotene (n = 73) or placebo (n = 95) daily for twenty one days prior to participation in the event. The pre-race training status, state of health and dietary vitamin and mineral intake of the athletes and their age matched controls were recorded by means of a questionnaire completed prior to the race. Runners with a history of allergies were excluded. The total pre-race vitamin intakes were calculated from the dietary intake, additional supplements taken by the athletes and the anti-oxidants given to the subjects.

Two weeks after the race, all participants were telephonically questioned regarding their compliance to the trial as well as the incidence and duration of the upper respiratory tract symptoms. Only reports of single upper respiratory tract symptoms lasting more than a day or a combination of at least two upper respiratory trace symptoms each which lasted less than a day were included in the final analysis. The

difference between the incidence of symptoms of infection in the runners ingesting placebo (40.4%) and the sedentary matched controls (24.4%) was not significantly different. The lowest incidence of symptoms of infection was reported in the Vitamin C group (15.9%) and this was significantly different from the placebo group ($p < 0.05$). This group reported a Vitamin C intake of 1004mg. The incidence of symptoms in the Vitamin C, E and Beta carotene group (20%) was also significantly lower than the placebo group. However, the incidence of symptoms in the Vitamin C and E group was not significantly different from that in the placebo group (Figure 2.7).

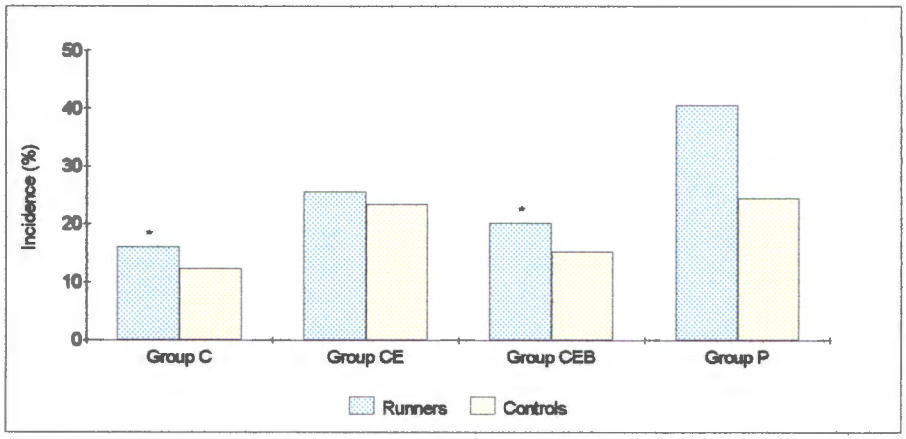

Figure 2.7: The incidence of symptoms of URT infection in runners (n = 178) and controls (n = 162) during the 14 day post race period. (Group C = Vitamin C 500mg, Group CE = Vitamin C 500mg & Vitamin E 400iu, Group CEB = Vitamin C 300mg, Vitamin E 300iu & Beta Carotene 18mg and Group P = placebo). Significant difference: *p < 0.05 (runners versus controls).

Adapted from Peters et al, 1996.

The findings of this study indicate that large intakes of Vitamin C alone (> 1000mg) are more effective than combinations of Vitamin E, Vitamin C and beta carotene in decreasing the incidence of symptoms of upper respiratory tract infection in ultradistance runners. In this study, no relationship between running time and incidence of upper respiratory tract symptoms was documented. Training status appeared to be an important factor and the highest incidence of symptoms was documented in runners who had done the least pre-race training (Figure 2.8). The training status ratio of each runner was calculated using the following formula:

$$\frac{\textit{Weekly training distance (km)} \times \textit{no. of weeks spent in training}}{\textit{average speed at which those kilometres were covered}}$$

Runners who reported a ratio of > 450 constituted the high-training status category, whereas those with a ratio < 300 were classified in the low-training status category.

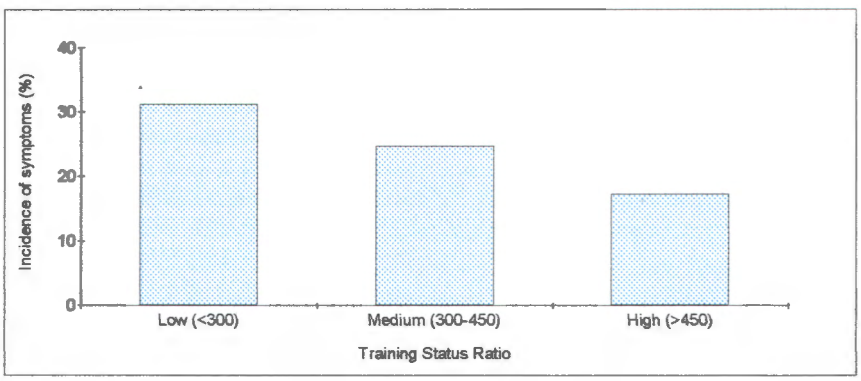

Figure 2.8: The incidence of post-race URTI symptoms in low, medium and high training status groups (n = 176).

Adapted from Peters et al, 1996.

An epidemiological survey investigating the relationship between self reported symptoms of infections, training data and participation the race has been conducted on applicants of the Los Angeles Marathon (Nieman et al, 1990). Eight days before the marathon, 4 926 of the 12 200 applicants were randomly selected and a previously validated 4-page questionnaire was sent to the subjects. There were 2 311 respondents (46.91%) and the study matched for age, marital status and reported sickness in other members of the runner's home. The main finding of the study was that 12.9% of participants reported an infectious episode in the week following the race compared to 2.2% of the control group of runners with similar age and marital status who did not participate (Figure 2.9). It was also shown that runners training more than ninety six kilometres per week were twice as likely to develop an infectious episode compared to those training less than thirty two kilometres per week in the two month pre-race period. The results therefore suggest that runners have an increased risk of developing an infectious episode during high intensity training or following a marathon race.

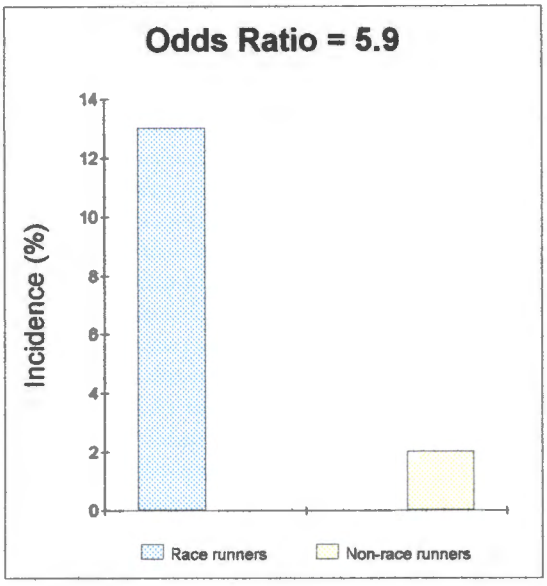

Figure 2.9: Self-reported URT infection in 2 311 Los Angeles marathon runners during the week following the 1987 Los Angeles Marathon.

Adapted from Nieman et al, 1990.

This tendency towards an increased incidence of upper respiratory tract symptoms in endurance runners has not however been found in events shorter than 42 kilometres. The incidence of infectious episodes in 273 runners two months before and one week after a 5km, 10km and 21km race in California has been investigated (Nieman et al, 1989). It was found that 25% of runners training more than twenty five kilometres per week reported at least one infectious episode as compared with 34.3% of runners training less than twenty five kilometres per week ($p = 0.09$). Only 6.8% of the runners preparing for the half marathon reported illness as compared to

17.9% of the 5km and 10km runners ($p = 0.067$). During the week following these races, runners did not report an increase incidence of infectious episodes compared with the week prior to the race. It was concluded that runners with a more serious commitment to regular exercise were less likely to develop infectious episodes than recreational runners. In addition, participating in a 5, 10 or 21km race did not appear to increase the risk of acquiring upper respiratory tract infection (Nieman et al, 1989).

Other studies (Heath et al, 1991; Nieman 1990; Nieman 1993) have investigated the relationship between long term training and the risk of developing symptoms of upper respiratory tract infection in runners. A cohort of five hundred and thirty male and female runners were followed up over a period of twelve months (Heath et al, 1991). The aims of the study were firstly, to document the incidence of upper respiratory tract infection, secondly, to examine possible risk factors associated with the development of infection and thirdly, to document the association between the amount of running and racing experience to infection in the athletes. Information about their illness was collected by self-report and runners were asked to indicate each day whether they had any of the following symptoms: cold (runny nose, sore throat or cough), allergy (itchy eyes or stuffy nose), headache, fever, nausea, vomiting, diarrhoea, fatigue/tiredness, muscle/joint/bone problem or injury and menstrual cramps. It is important to emphasise that the analyses were based on self reported symptoms and that subsequent studies could be strengthened by confirming the diagnosis of illness as well as measuring the immune status.

The outcome measure for the analysis was an upper respiratory tract infection defined as self reported symptoms (runny nose, sore throat or cough) for two consecutive days. An episode was considered to be a new upper respiratory tract infection if it was separated from a previous upper respiratory tract infection by at least three days without any respiratory symptoms. Episodes that were due to allergy or chronic respiratory symptoms were not considered as an infection and excluded from the analysis. Risk factors related to the runners were investigated and included number of days run per week, number of miles run daily and annually, racing history and marathon participation.In addition, age, gender, marital status, smoking status, alcohol use, breakfast habits, vitamin use, dietary supplements, sleep, number of people in the household and body mass index were also considered as potential risk factors for the development of upper respiratory tract symptoms.

The average number of upper respiratory tract infections per person per year for the cohort was 1.2. Upper respiratory tract infection was indicated by the presence of any of the following symptoms: runny nose, sore throat or cough. The lowest odds ratio for upper respiratory tract infection was documented in those athletes running less than sixteen kilometres per week. The odds ratio more than doubled for those running more than twenty seven kilometres per week, demonstrating that total annual running distance was a significant risk factor for upper respiratory tract symptoms. The risk of upper respiratory tract infection increased as weekly running mileage increased. Runners living alone were also found to be at increased risk for

upper respiratory tract infection. A BMI (body mass index = weight in kg / height in m^2) greater than the 75 percentile was associated with a smaller likelihood of having an event, as was being male. Finally, the association between alcohol users and upper respiratory tract infections was positive in males and negative in females. Lack of vitamin intake, not eating breakfast, smoking and sleeping either less than seven or greater than eight hours a night were unrelated to the incidence of upper respiratory tract infection in this study.

Further evidence that the risk for developing symptoms of upper respiratory tract infection may be related to the volume of training may be found in two other studies (Nieman et al, 1993; Nieman et al, 1990). In a randomised controlled study (Nieman et al, 1990), thirty six mildly obese inactive women performed five, forty five minute walking sessions per week for fifteen weeks. This resulted in a significant reduction ($p < 0.05$) of self reported upper respiratory tract symptoms in the active group compared with a sedentary control group with less than 50% of the number of days with symptoms in the active versus the control group (Figure 2.10).

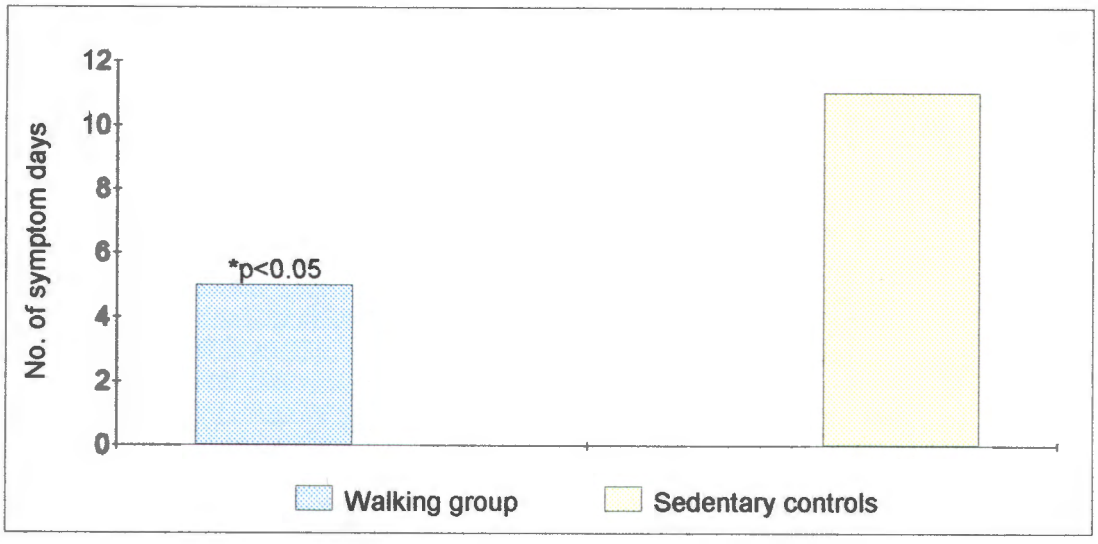

Figure 2.10: **The effects of moderate exercise training on the total number of URT symptom days during a 15 week period in walkers and controls. Significant difference: * $p < 0.05$.**

Adapted from Nieman et al, 1990.

In another study, a group of highly conditioned (n = 12) elderly female subjects exercised moderately on a daily basis for about one and a half hours. They were compared over a twelve week period to a group walking for forty minutes, five times per week (n = 14) and a control group who participated in calisthenic exercises (n = 16) only. Using a daily log of self reported upper respiratory tract symptoms, the lowest incidence (8%) was documented in the highly conditioned training group.

The walkers reported an incidence of 21%, whereas the control group had the highest incidence of 50% (Figure 2.11). The study therefore suggests that moderate exercise may improve immune function and decrease the risk for developing symptoms of upper respiratory tract infection.

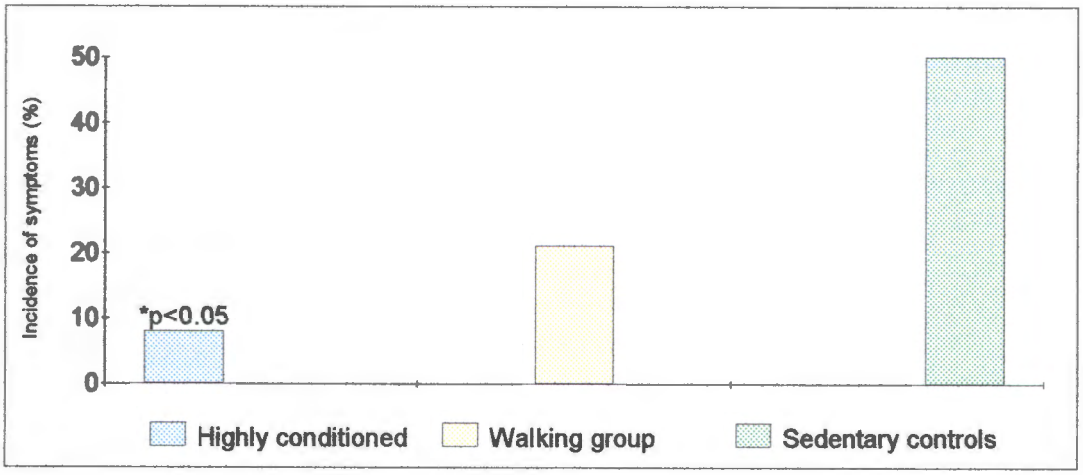

Figure 2.11: The incidence of URT infection (% of subjects with symptoms) during a 12 week study in highly conditioned, walking, and sedentary control groups of elderly women

Adapted from Nieman et al, 1993.

It has been suggested that the relationship between exercise and upper respiratory tract infection is "J" shaped (Nieman, 1994), where the risk of upper respiratory tract infection is at the lowest in someone engaging in moderate exercise training (Figure 2.12). The risk then rises in subjects performing excessive amounts of high intensity exercise.

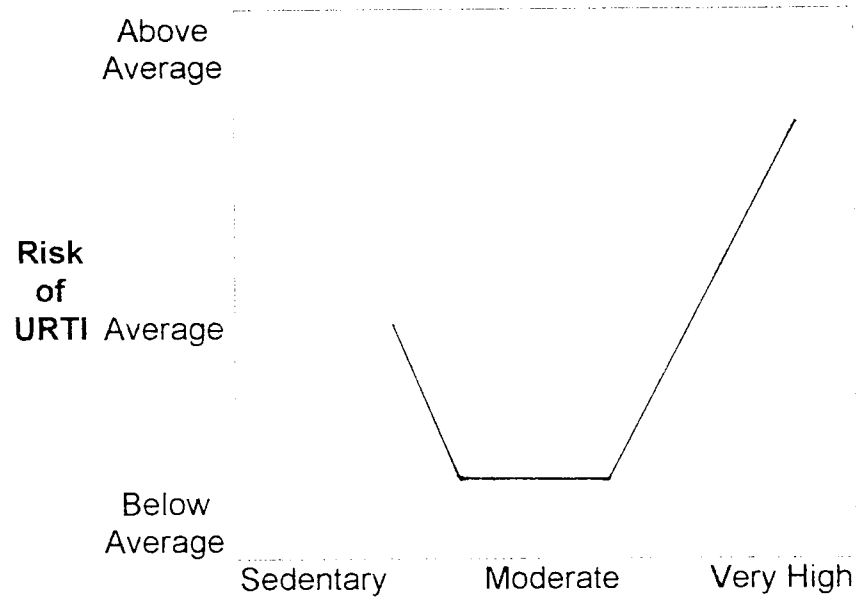

Figure 2.12: "J"-shaped model of relationship between varying amounts of exercise and risk of URTI in runners (27). This model suggests that moderate exercise may lower risk of respiratory infection while excessive amounts may increase the risk.

Adapted from Nieman, 1994.

The "J" shaped relationship between exercise and the risk of URTI seems to be less consistent in studies reported in athletes other than runners. One hundred and twenty one male and fifty three female cross country skiers, either members of the Swedish national teams or young elite skiers studying at sports college, were studied for a twelve month period (Berglund et al, 1990). The frequency, types of

infection, and to what extent they caused absence from training was investigated. All types of infectious disease that caused absence from training for 3 days or more were included. The diagnosis was made by a medical doctor in 29% of cases, a coach in 4%, and by the athletes themselves in the remaining 67% of cases. Upper respiratory tract infection was the most common infection causing absence from training (92.3%). There was however, no significant incidence of infection between the world class cross country skiers (1.5 infections per subject per year) and the young elite skiers (1.88 infections per subject per year). Furthermore, the incidence was similar to that in the general population.

The incidence of upper respiratory tract infections was also studied in a group of 44 elite orienteers and 41 non-athletes who were matched for age, sex and occupation (Linde, 1987). This was a prospective study which was conducted over one year with the subjects diarising self-reported symptoms. The orienteers reported 2.5 episodes of upper respiratory symptoms per year which was significantly higher ($p < 0.05$) than the 1.7 episodes reported by the non-athlete group. The symptoms also lasted longer in the orienteers compared with the control group (7.9 days vs. 6.4 days). One third of the controls reported no infection during the study period, while only 10% of orienteers reported no infection. The orienteers also showed a more equal distribution of illness over the year when compared to the non-athletes who showed the typical winter peak. The relationship between the incidence and duration of symptoms of upper respiratory tract infection and the habitual level of physical activity in 92 men and 107 women participating in the Amsterdam Growth

and Health study has also been reported (Schouten et al, 1988). The weekly "dose" of physical activity was quantified as the product of duration of exercise (min/week) and weekly energy expenditure (measured as METs/week). A limitation of the study was that the upper respiratory tract infection measurement relied on memory recall over the past six months. When comparing groups by total energy expenditure, level of sports activity or maximum aerobic power, no difference in the incidence or duration of upper respiratory tract symptoms was documented. However, a slight negative correlation between the incidence of symptoms and a moderate level of sports participation in female participants was reported.

In a prospective study conducted on twelve year old children (n = 62) participating in swimming, ice hockey and gymnastics four times a week, no difference in the incidence of infection between these children and an age-matched controlled group were reported (Osterback et al, 1987).

The prevalence of illness and absence in members of three men's intercollegiate athletic teams (wrestlers, swimmers and gymnasts) was also studied (Strauss et al, 1986). Members (n = 87) were interviewed weekly over eight weeks. Eighty six percent of the athletes had at least one respiratory illness during the study period. The study was conducted during the peak season (winter) for respiratory illness. There were no significant differences among teams for respiratory problems. One of the major limitations of this study was that there was no control group of non-athletes.

In summary, epidemiological studies in ultradistance runners show that these athletes are at increased risk for developing symptoms of upper respiratory tract infection during times of intense training and especially so, in the two weeks after an ultramarathon event. These findings have been largely based on self-reported symptoms, either by questionnaire or telephonic interview, without a clinical or laboratory diagnosis of actual infection. Athletes that engage in moderate activity do not appear to be at increased risk for upper respiratory tract infection and in some instances may show resistance to the development of upper respiratory infection.

2.4. Fusafungine and the prevention or treatment of upper respiratory tract infection

Fusafungine is an antibiotic of fungal origin which is extracted from Fusarium literatum WR, strain 437. It has three fundamental pharmacological properties:

1. It is a local antibiotic adapted to the treatment of respiratory tract infections with antimicrobial activity against the majority of bacteria responsible for these infections (German-Fattal, 1996). In addition, it has an anti-fungal action (which limits the risk of secondary candidiasis).

2. It has a potent anti-inflammatory action which reduces oedema and exudation thereby relieving inflammatory obstruction and pain (German-Fattal et al, 1995; Gosset et al, 1996). As this action is intrinsic to the drug, without the addition of corticosteroids and vasoconstrictors, there is no risk of a rebound effect or habituation.

3. It is a true micronised aerosol with micron-sized particles that diffuses throughout the respiratory tract, deeply penetrating and lining the mucous membranes (Newman, 1995). It has no systemic effects.

It can be hypothesised that the local anti-inflammatory and the local anti-microbial action of fusafungine may reduce the incidence of upper respiratory tract infection in runners prior to and after completion of an ultramarathon. Although upper respiratory tract infections are most commonly caused by viruses, fusafungine would also be expected to have an effect on the development of secondary bacterial infection. The anti-inflammatory action may also reduce upper respiratory tract symptoms as opposed to infection and this would also have to be considered when assessing its overall effect.

Chapter 3

The effect of fusafungine on the incidence of upper respiratory tract infection in ultradistance runners

3.1. Introduction

Ultradistance athletes have been shown to have increased incidence of upper respiratory tract symptoms after an event (Nieman et al, 1990; Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996). This increased incidence has been documented by self reported symptoms without clinical examination or laboratory documentation of infection (Nieman et al, 1990; Nieman et al, 1991; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996). Furthermore, it has been shown that faster athletes(Peters, 1983) and those who have trained harder were more at risk for developing symptoms (Heath et al, 1991; Nieman et al, 1990; Peters et al, 1983; Peters et al, 1993).

Various investigators have studied the relationship between exercise and immune function. In general, detrimental changes to the immune system can be documented in response to very high intensity exercise, or excessively prolonged exercise bouts (Mackinnon et al, 1987; Mackinnon et al, 1993; Nieman et al, 1992; Nieman et al, 1989; Weight et al, 1991). However, no specific immunological marker has been found to account for this increased incidence of upper respiratory tract symptoms in ultradistance runners.

Fusafungine has both antibacterial and anti-inflammatory properties and may be of benefit to decrease the incidence of upper respiratory tract symptoms and infections in ultradistance runners. This study was conducted to determine whether the use of fusafungine before and after an ultradistance event would reduce the incidence of respiratory tract symptoms in the athletes. In addition, evidence of true infection as opposed to symptoms was sought by means of clinical examination and laboratory documentation of the infective agent.

3.2. Aim of the study

The aim of this study was to determine whether the use of a topical anti-inflammatory/antibacterial agent (fusafungine) will decrease the incidence of respiratory tract infections and respiratory tract symptoms before and after an ultradistance running event.

3.3. Methodology

3.3.a. Type of study

This study was conducted as a randomised double blind placebo controlled clinical trial. The subjects of the study were familiarised with the details of the clinical trial and signed informed consent was obtained. Ethics and Research Committee approval by the Ethics and Research Committee of the University of Cape Town was obtained prior to the onset of the study.

3.3.b. Subject recruitment

A homogeneous group of male runners (n = 96) who took part in the 1996 Two Oceans Ultramarathon (56 kilometres) were recruited by convenience sampling for the study. The following inclusion criteria applied:

-Runners who have either completed a 56 kilometre ultramarathon in less than five and a half hours or a marathon qualifying time of less than three and a half hours.

-Runners with a body mass index (BMI) of less than the 75th percentile.

-Runners with no history of severe illness requiring long term medication.

-A history of restricted use of anti-oxidants. This was defined as runners who do not consume large doses of anti-oxidant supplements on a daily basis (Vitamin C < 1000mg, Beta Carotene < 18mg and Vitamin E < 400IU).

3.3.c. Dietary food and supplement intake

A three day dietary analysis was performed on a randomly selected sub-group of runners (n = 44) to document their intake of nutrients, in particular, anti-oxidants. The subjects were instructed to document all foods, fluid and vitamin or mineral supplements that were consumed for three consecutive days (Appendix 3). A three day food diary was used as opposed to a five or seven day diary to ensure a high compliance from participants. The subjects were asked to quantify all foods and fluid consumed in standard serve sizes such as cups, tablespoons or teaspoons. Protein foods were described according to actual weight or in terms of their size in relation to the number of match boxes. Food preparation and method of cooking were also

taken into consideration to ascertain the fat content of foods. On completion of the food diaries, all subjects were then telephoned after the event to verify the standardised food servings and quantities documented. The three day food records were then analysed by a sports dietician and converted into nutrients using the Food Fundi Professional (Penta Medical Systems, Johannesburg, South Africa) computer program.

3.3.d. Administration of medication

The original group of runners (n = 96) was randomly allocated to either a group receiving active medication (fusafungine) (active group) or a group receiving placebo medication (control group) in a double blind manner. All the runners completed a pre-race questionnaire one week before the event (Appendix 1). This questionnaire provided details regarding the personal details of the runner, training history and medical history including history of previous upper respiratory tract infections.

Active and placebo medication in identical containers were pre-packed and labelled by the pharmaceutical company (Servier Laboratories, P.O. Box 930, Rivonia 2128, Republic of South Africa). Both the subjects and the investigators were blinded with respect to the medication they received or administered. The code was kept sealed and only revealed once statistical analysis was complete. Subjects who complained of symptoms of upper respiratory tract infection on entry to the trial were excluded from further participation.

Subjects were required to self-administer the spray for two days prior to (Days -2 to -1) and for nine days after the race (Days 0-9). The dosage was four sprays into each nostril four times daily, and four sprays into the throat while inhaling, also four times daily in order to obtain the best possible compliance. The subjects were familiarised with the proper use of the spray, by carefully instructing them, and by providing them with a standardised instructional pamphlet. The subjects completed a patient diary on a daily basis, documenting their dosage administration over the twelve day period, as well as the development of respiratory tract symptoms (Appendix 2). The sequence of events is summarised in Figure 3.1.

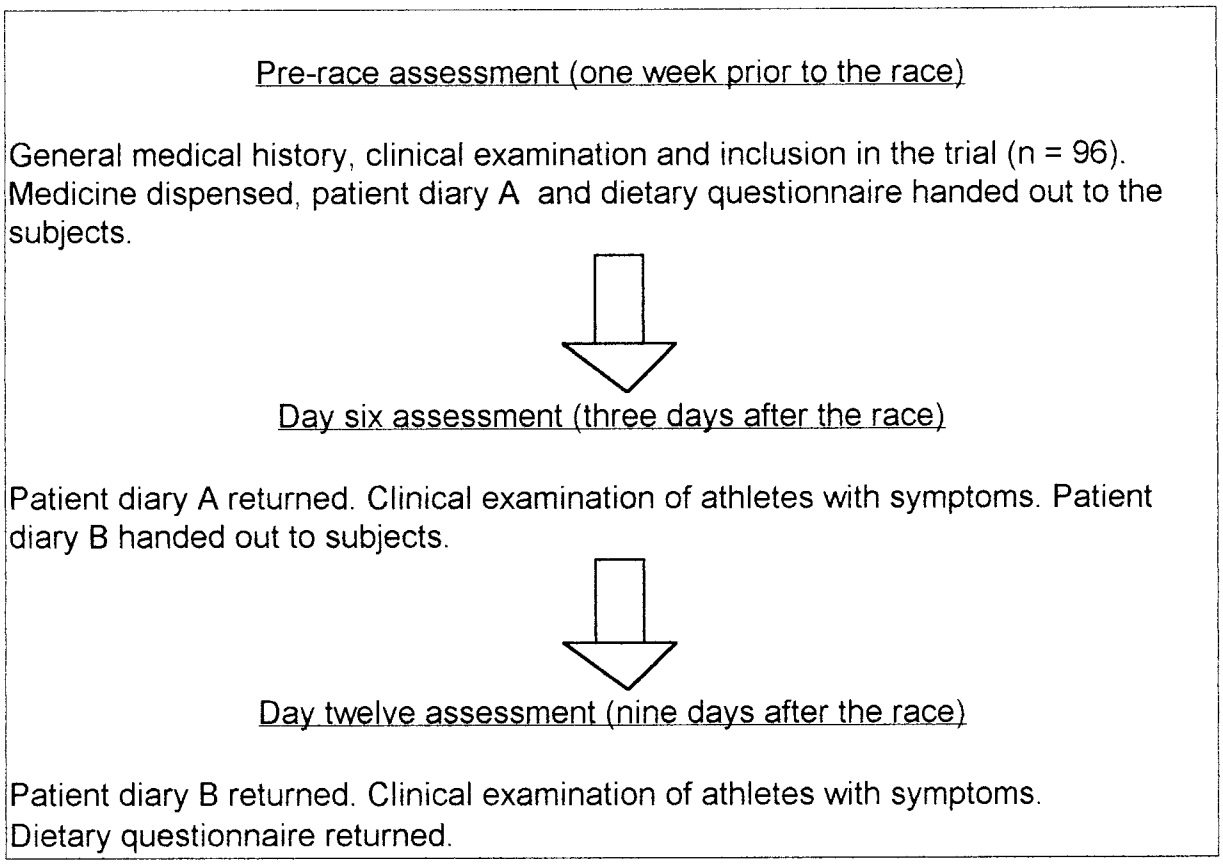

Figure 3.1: Methodology: Subject assessment (pre- and post-race).

Adequate compliance to medication use was defined as > 70% of all the dosages of the active medication (active group) over the treatment period. After the study was completed, subjects who recorded less than 70% administration of all the dosages over the treatment period were excluded from the active group. Six subjects were excluded from the active group because of poor compliance. The final group numbers were therefore as follows; Active (n = 42), and Control (n = 48).

Running intensity in the two groups was determined by the average minutes/kilometre during training, and the final running times for the fifty six kilometre ultradistance event. These parameters were recorded and compared between the two groups.

3.3.e. Incidence of respiratory tract infections and symptoms

All the subjects were required to report any symptoms of respiratory tract infections (upper and lower) to the investigators. Once a runner presented with any symptom, the runner visited the laboratory where a clinical history and examination was conducted. All the subjects who presented with a sore throat were subjected to a throat swab and a viral gargle. The throat swab was cultured and inoculated for bacteria in a standard microbiology laboratory (Drs. Dietrich, Street and Partners, Cape Town). Using a large blood agar plate with a bacitracin disc and incubated at 37 °C (anaerobic culture). Furthermore, a Todd-Hewitt broth was incubated at 37 °C (aerobic culture) and a subculture Todd-Hewitt broth onto blood agar with a bacitracin disc after 18 hours.

A solution for the viral gargle (7,5% sucrose, 100mmol phosphate buffer and 0,002% phenol red) was obtained from the Department of Virology of the University of Cape Town, Medical School. Each symptomatic subject gargled thoroughly with the solution which was then returned to the bottle and transported on ice to the laboratory. Each sample was innoculated into duplicate primary African Green Monkey kidney cell cultures and incubated and observed for 10 days. At the end of

this period the cultures were tested for Haemadsorption properties with guinea pig red blood cells. Coverslip cultures were stained and examined by microscopy for viral cytopathic effects (Prof. Moodie - personal communication).

For the purpose of this study, athletes who presented with symptoms but negative viral or bacterial cultures, were classified as "athletes with respiratory tract symptoms but no infections", and athletes with generalised symptoms (malaise, fever, headaches) and a positive throat swab or a positive viral culture were regarded as "athletes with respiratory tract infections".

Symptoms that were recorded were blocked nose, runny nose, sore throat and cough. In order to make comparisons to previously published studies, symptoms were subdivided into nasal symptoms (blocked nose and runny nose), upper respiratory tract symptoms (blocked nose, runny nose and sore throat) and all respiratory tract symptoms (blocked nose, runny nose, sore throat and cough).

3.3.f. Statistical analysis of data

Statistical analysis was conducted at the Institute for Biostatistics at the Medical Research Council, in Parow, Cape Town. Standard descriptive statistics were used to document the characteristics of the groups, and the Chi-square test or the Fisher's exact test were used to determine whether significant differences in frequencies of variables occurred between the two groups. The level of significance was established at $p < 0.05$.

3.4. Results

3.4.a. Subject characteristics

The physical characteristics, training history and running intensity of the subjects that were recruited for the study (active and placebo groups) are depicted in Table 3.1. There were no significant differences between the two groups with respect to age, weight, height, weekly training (km/week) and running intensity (running speed and finishing times). There were also no significant differences between the two groups with respect to the frequency of a past history of respiratory disorders, hay fever, asthma, smoking and average number of respiratory tract infections per year. The dietary intake of energy, fat, protein, carbohydrate, Vitamin A, Beta carotene, Vitamin C and Vitamin E was not significantly different between groups (Table 3.2).

3.4.b. Incidence of respiratory tract symptoms

The incidence of a blocked nose in the two groups of ultradistance runners is depicted in Figure 10. There was no significant difference in the incidence (incidence per 100 runners) between the active and the placebo groups for the three time periods that were studied.

The incidence of a runny nose in the ultradistance runners in the three times periods that were studied is depicted in Figure 3.3. There was no significant difference in the incidence of a runny nose in the two groups in any of the time periods that were studied.

The incidence of a sore throat in ultradistance runners in the three time periods that were studied is depicted in Figure 3.4. There was no significant difference in the incidence of sore throat between the two groups in any of the time periods that were studied.

The incidence of a cough in ultradistance runners in the three time periods that were studied is depicted in Figure 3.5. There was no significant difference in the incidence of cough between the two groups in any of the time periods that were studied.

The incidence of nasal symptoms (blocked nose or runny nose) in ultradistance runners in the two groups over the three time periods that were studied is depicted in Figure 3.6. There was no significant difference in the incidence of nasal symptoms between the two groups in the time periods day -2 to -1, and day 4-9. However, there was a tendency for a significant decrease ($p = 0.085$) in nasal symptoms in the active group in the time period 0-3 days after the ultradistance race.

The incidence of all respiratory tract symptoms (blocked nose, runny nose or sore throat) in ultradistance runners in the three time periods in the two groups that were studied is depicted in Figure 3.7. There was a significantly lower ($p = 0.025$) incidence of upper respiratory tract symptoms in the active group (17%) compared to the control group (40%) in the time period 0 to 3 days after the race. There was

no significant difference in the incidence of upper respiratory tract symptoms in the two groups in days -2 to -1 (before the race) and in days 4 to 9 (after the race).

The incidence of all respiratory tract symptoms in ultradistance runners in the three time periods that were studied is depicted in Figure 3.8. There was a significantly lower incidence of respiratory tract symptoms in the active group compared to the placebo group in the time period 0 to 3 days after the race ($p = 0.028$). There was no significant difference in the incidence of respiratory tract symptoms in the two groups in the time period -2 to -1 (before the race) and day 4 to 9 (after the race).

The incidence of all post-race respiratory tract symptoms in the ultradistance runners in the time period day 0 to 9 after the race is depicted in Figure 3.9. There was no significant difference in the incidence of all post-race respiratory tract symptoms between the two groups.

In none of the subjects presenting with a sore throat, were positive bacterial or viral cultures documented. Therefore the incidence of upper respiratory tract infections is zero.

3.4.c. Incidence of clinical findings

Twelve subjects presented with symptoms at the day six assessment. No athlete had either an elevated temperature or pulse rate. Eight had a mild pharyngitis and all had clear lungs on physical examination. One subject presented on day twelve with mild pharyngitis and ronchi at the left lung apex. His temperature and pulse rate

were normal.

3.4.d. The effect of training volume and finishing times on the incidence of respiratory tract symptoms

The runners (n = 96) were grouped into those who had any symptoms irrespective on which day (n = 48) and those who were symptom-free (n = 48). The symptom-free athletes did significantly ($p < 0.05$) less training than those with symptoms as depicted in Figure 3.10. There was no significant difference between the groups with regard to their finishing times ($p > 0.05$) as depicted in Figure 3.11.

3.5. Discussion

This is the first study of its kind that documents symptoms as well as objective evidence for the presence of an infection (clinical examination, viral gargles and bacterial cultures from throat swabs) in ultradistance runners after an event. Although a mild pharyngitis was found on clinical examination in nine athletes (9%), there was no evidence of actual viral or bacterial infection as documented by negative viral gargle cultures and bacterial cultures from throat swabs. In addition, although there were self-reported cases of fever in previous studies (Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996), none of the athletes presenting with symptoms demonstrated an elevated temperature or resting pulse rate in this study. It has always been postulated that runners presenting with symptoms after an endurance event suffer from infections, but this study fails to

support this hypothesis.

The incidence of upper respiratory tract symptoms in the time period 0 to 3 days after an ultradistance event was significantly decreased after the administration of a topical antibacterial/anti-inflammatory agent (fusafungine).

Fusafungine effectively reduced the incidence upper respiratory tract symptoms from 40% in the placebo group to 17% in the active group in the three days after the event. This occurred despite the fact that no evidence of bacterial or viral infection could be documented. It therefore appears that the mechanism by which fusafungine reduced the incidence of upper respiratory tract symptoms is by its local anti-inflammatory action on the nasal and pharyngeal mucosa alone.

Furthermore, the beneficial effect of fusafungine is only evident in the first three days after the ultradistance event. This implies that the inflammatory response was maximal in this time period which would be consistent if the "injury" occurred on the day of the race, resulting in a maximal acute inflammatory response in days 0-3. The pathological mechanism responsible for the production of upper respiratory tract symptoms after ultradistance events is not clear, but may be local inflammation, which is maximal in the first three days after the event. There is no evidence that the inflammatory response is due to infection, and may be due to mechanical irritation from dust or other particles, rapid air movement or drying of the respiratory mucosa by obligatory mouth breathing during the event.

In this study the incidence of upper respiratory tract symptoms in the placebo group in the first few days after an ultramarathon event was 40%. This is similar to the incidence of post-race symptoms in previous studies (Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996). As documented in other studies (Peters, 1990; Peters et al, 1993; Peters et al, 1996), nasal symptoms (blocked nose and runny nose) were most common, followed by a sore throat. In contrast, in their previous study at the Two Oceans Marathon (Peters et al, 1983), Peters and Bateman found that sore throat was the most prevalent symptom, followed by nasal symptoms. In all these studies (Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996) the authors did not differentiate between blocked or runny nose when documenting nasal symptoms.

High weekly mileage was associated with an increased risk for the development of upper respiratory tract symptoms. This is consistent with previous findings (Heath et al, 1991; Nieman et al, 1990; Peters et al 1983; Peters et al, 1993). In contrast, two other studies (Peters, 1990; Peters et al, 1996) found that athletes who did the least training had the highest incidence of post-race upper respiratory tract symptoms.

Upper respiratory tract infections, however, remain a real dilemma for ultradistance athletes. Until further research provides clarity regarding the relationship between upper respiratory tract symptoms and true infection in these athletes the following preventative measures are advised. Athletes should minimise exposure to pathogens by avoiding contact with infected individuals, especially children

(Shephard et al, 1993). Since viruses are often transmitted by hand contact, the hands should be washed regularly and any rubbing of eyes or nose should be avoided (Shephard et al, 1993). For those athletes engaged in high intensity training further preventative measures include spacing vigorous workouts and race events as far apart as possible, eating a well balanced diet, keeping life stresses to a minimum, avoiding over-training and obtaining adequate sleep (Heath et al, 1992). Vitamin supplementation (especially Vitamin C) may also be beneficial (Peters et al, 1993). Athletes may be innoculated against viruses endemic to the area where they may compete (Shephard et al, 1993). Muscular immunoglobulin injections may reduce the incidence, duration and severity of upper respiratory tract illness in athletes (Nieman et al, 1991).

Athletes who develop symptoms of upper respiratory tract infection are advised to follow a suggested "neck check" (Eichner, 1993) when deciding to exercise while infected. If all the symptoms are " above the neck" (runny or stuffy nose, scratchy throat), the athlete could begin their exercise routine at below normal intensity for ten minutes. If the activity made them feel worse, they should stop exercising, but if they feel better, they should continue with training. However, if any symptoms were "below the neck" (muscle aches, cough, vomiting, diarrhoea or fever) training should be discontinued (Eichner, 1993).

Finally, ultradistance runners who regularly suffer from upper respiratory tract symptoms post exercise can be advised to use a local anti-inflammatory agents

such as fusafungine to decrease the risk of developing symptoms. The duration of treatment should be limited to 3-5 days post event.

Table 3.1: Physical characteristics, training history and running intensity in the active and placebo groups (values are mean ± standard deviation).

	Active (n=42)	Placebo (n=48)
Age (years)	39 ± 8	38 ± 9
Height (cm)	177 ± 8	178 ± 8
Weight (kg)	76 ± 10	72 ± 8
Training volume (km/week)	66 ± 19	68 ± 22
Training speed (min/km)	4.96 ± 0.40	4.81 ± 0.5
56km finishing time (hrs)	5.1 ± 0.6	5.1 ± 0.6

No significant difference between groups

Table 3.2: Dietary intake of nutrients in the active and placebo groups (values are mean ± standard deviation).

	Active (n=19)	Placebo (n=25)
Energy (kJ)	10014 ± 2470	15349 ± 20758
Fat (g)	97 ± 37	110 ± 36
Protein (g)	91 ± 18	102 ± 36
Carbohydrate (g)	262 ± 68	305 ± 98
Vitamin A (iu)	1327 ± 726	2072 ± 2237
Beta Carotene (mg)	8 ± 4	10 ± 7
Vitamin C (mg)	616 ± 599	702 ± 611
Vitamin E (iu)	25 ± 21	28 ± 22

No significant difference between groups

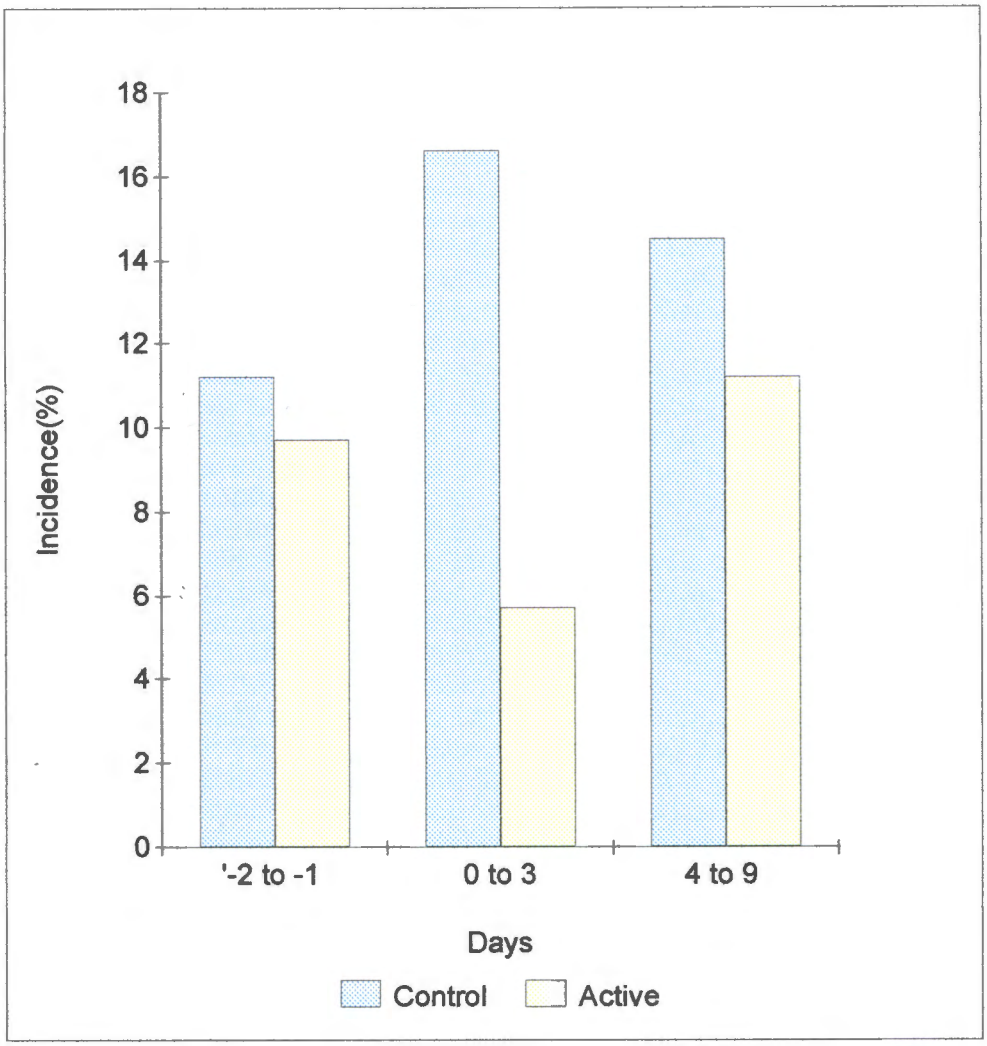

Figure 3.2: Incidence of blocked nose in ultradistance runners (n = 90). No significant difference between groups.

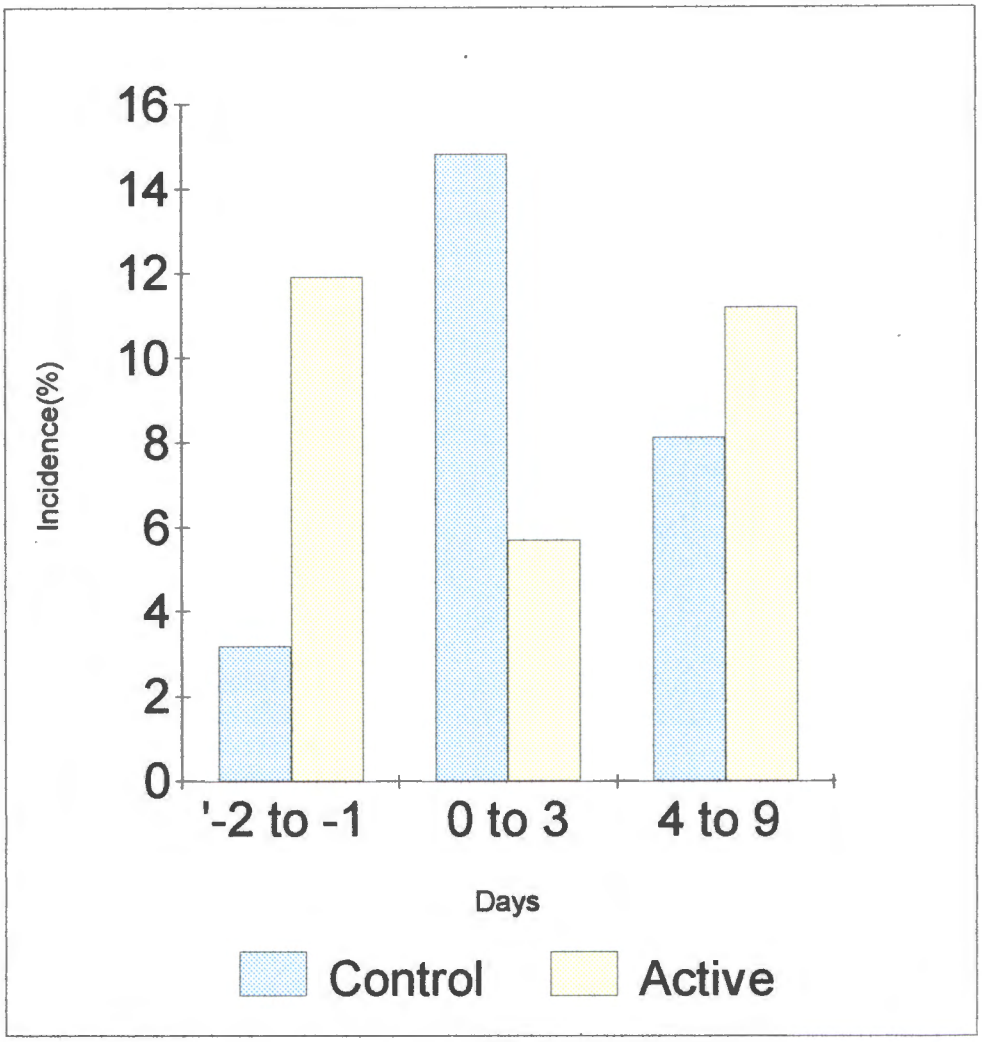

Figure 3.3: Incidence of runny nose in ultradistance runners (n = 90). No significant difference between groups.

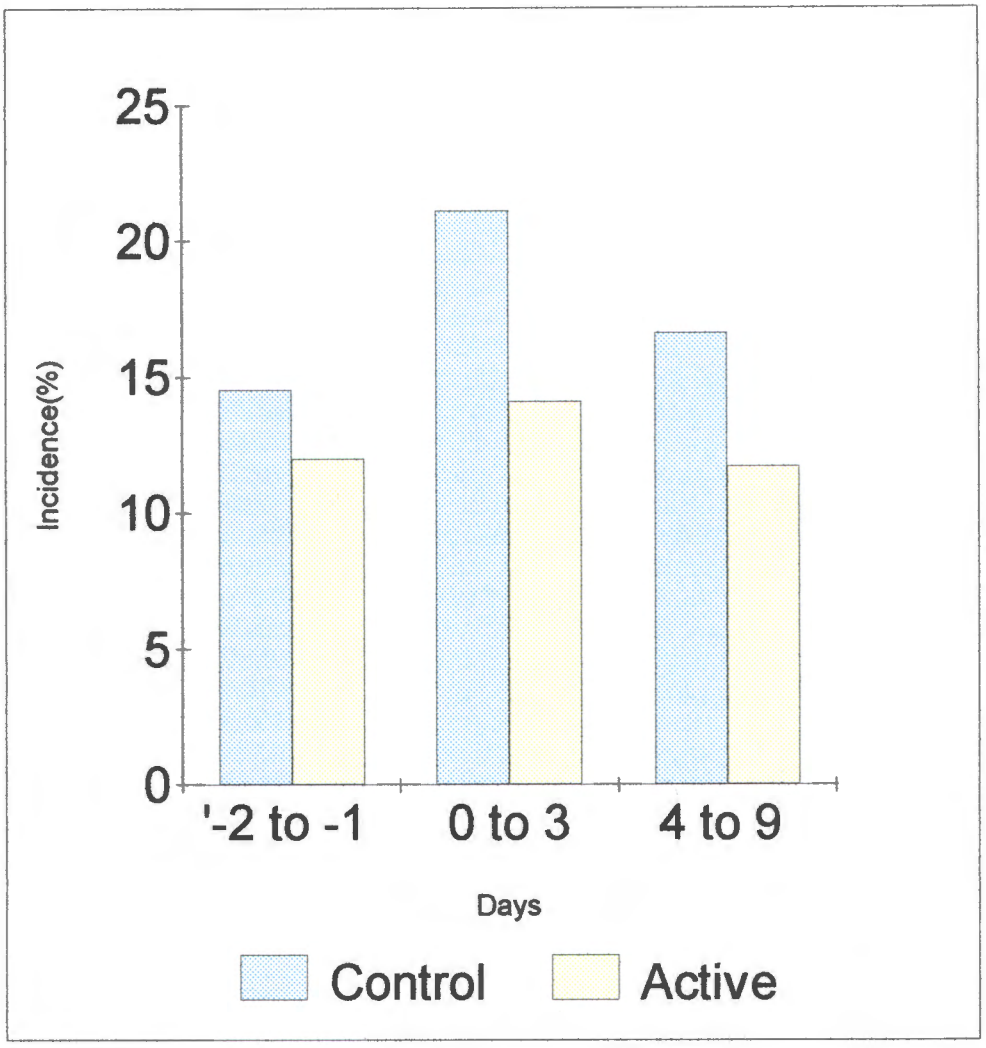

Figure 3.4: Incidence of a sore throat in ultradistance runners (n = 90). No significant difference between groups.

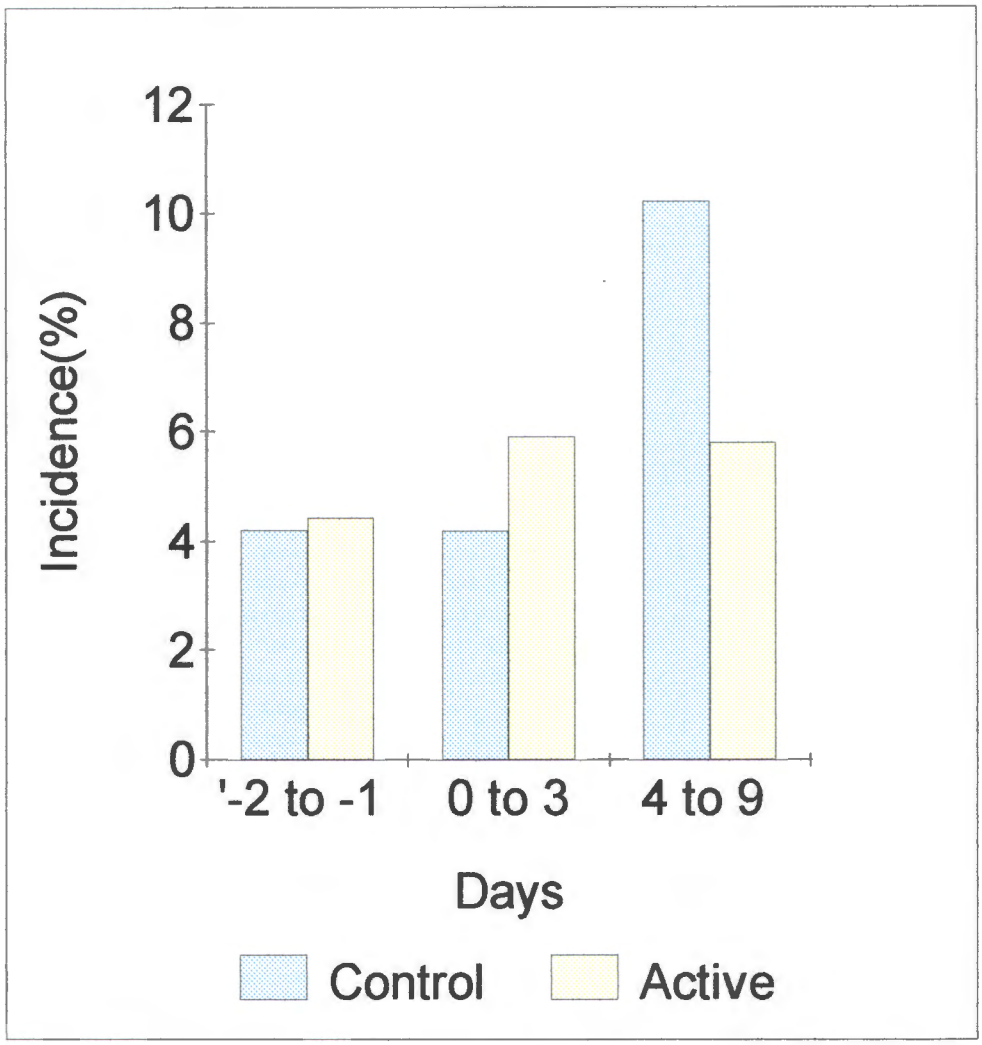

Figure 3.5: Incidence of a cough in ultradistance runners (n = 90). No significant difference between groups.

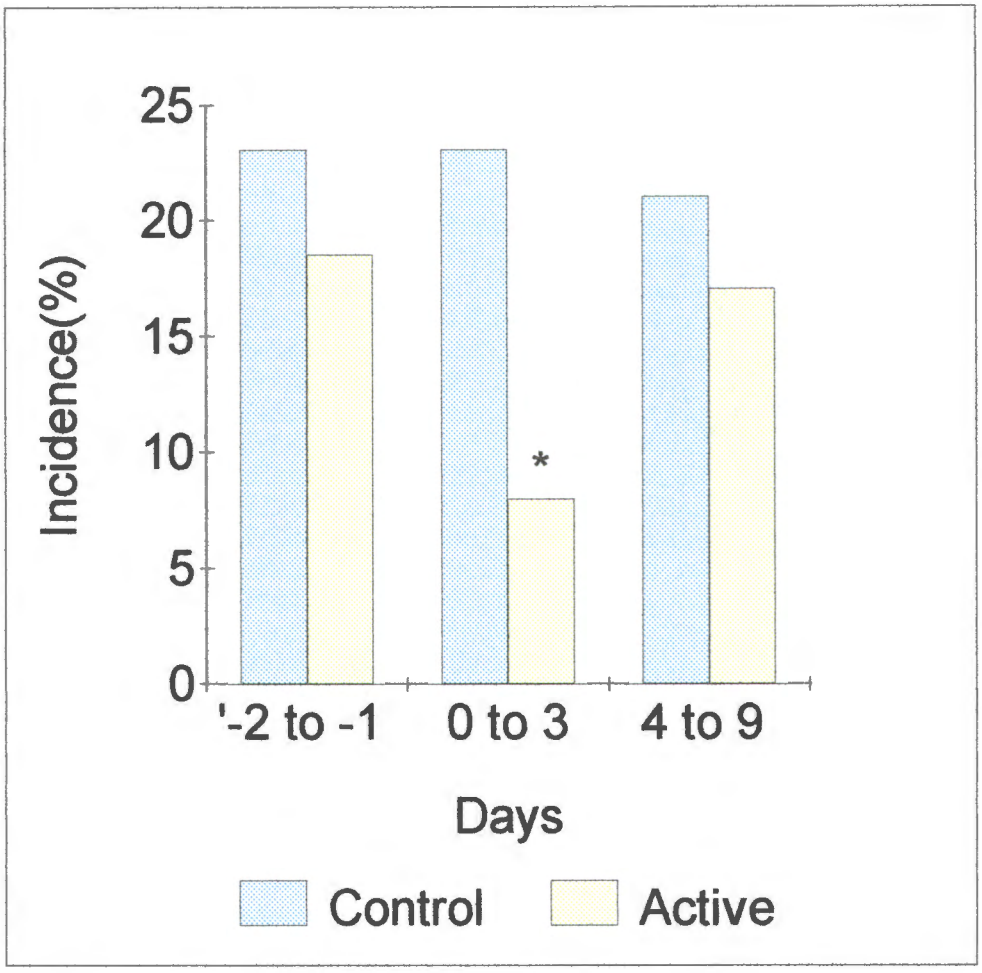

Figure 3.6: Incidence of nasal symptoms in ultradistance runners (n = 90). No significant difference between groups (* p = 0.085).

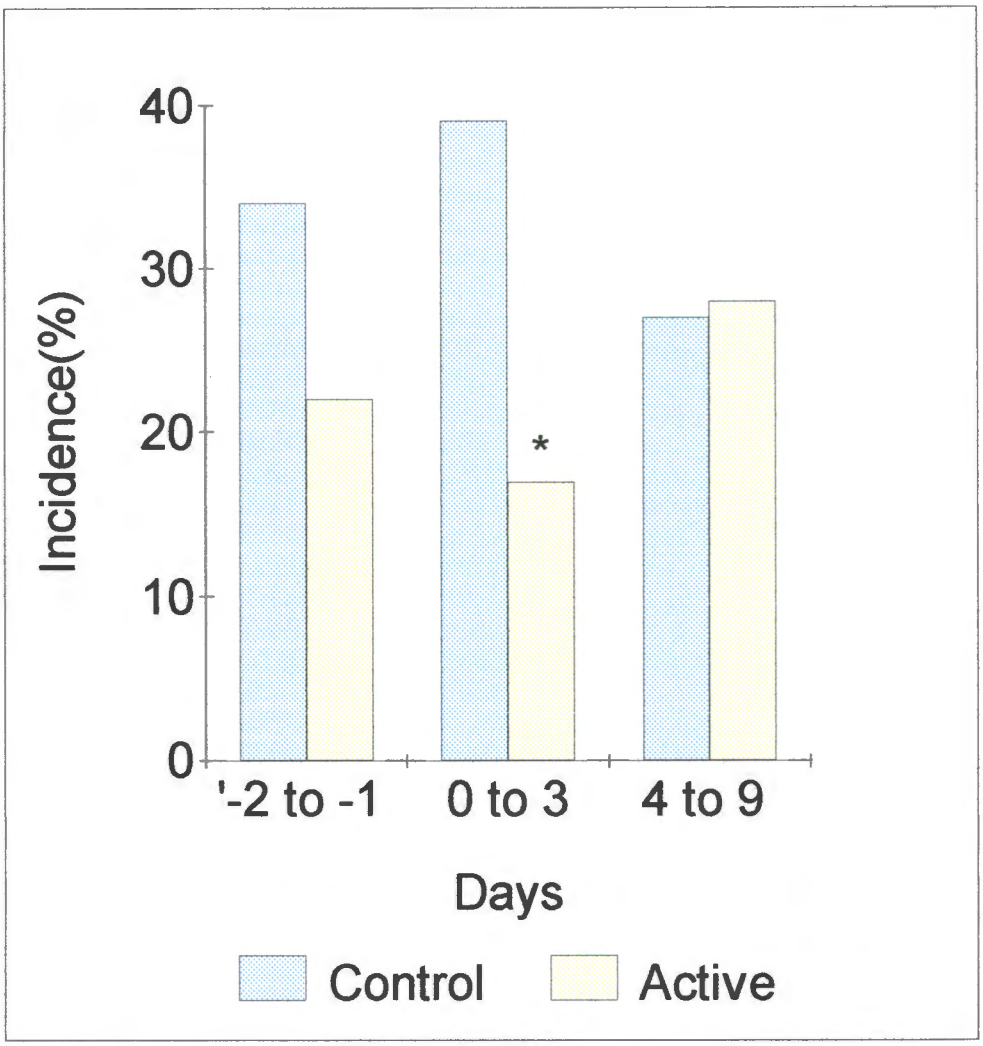

Figure 3.7: Incidence of upper respiratory tract symptoms in ultradistance runners (n = 90). Significant difference between groups (* p = 0.025).

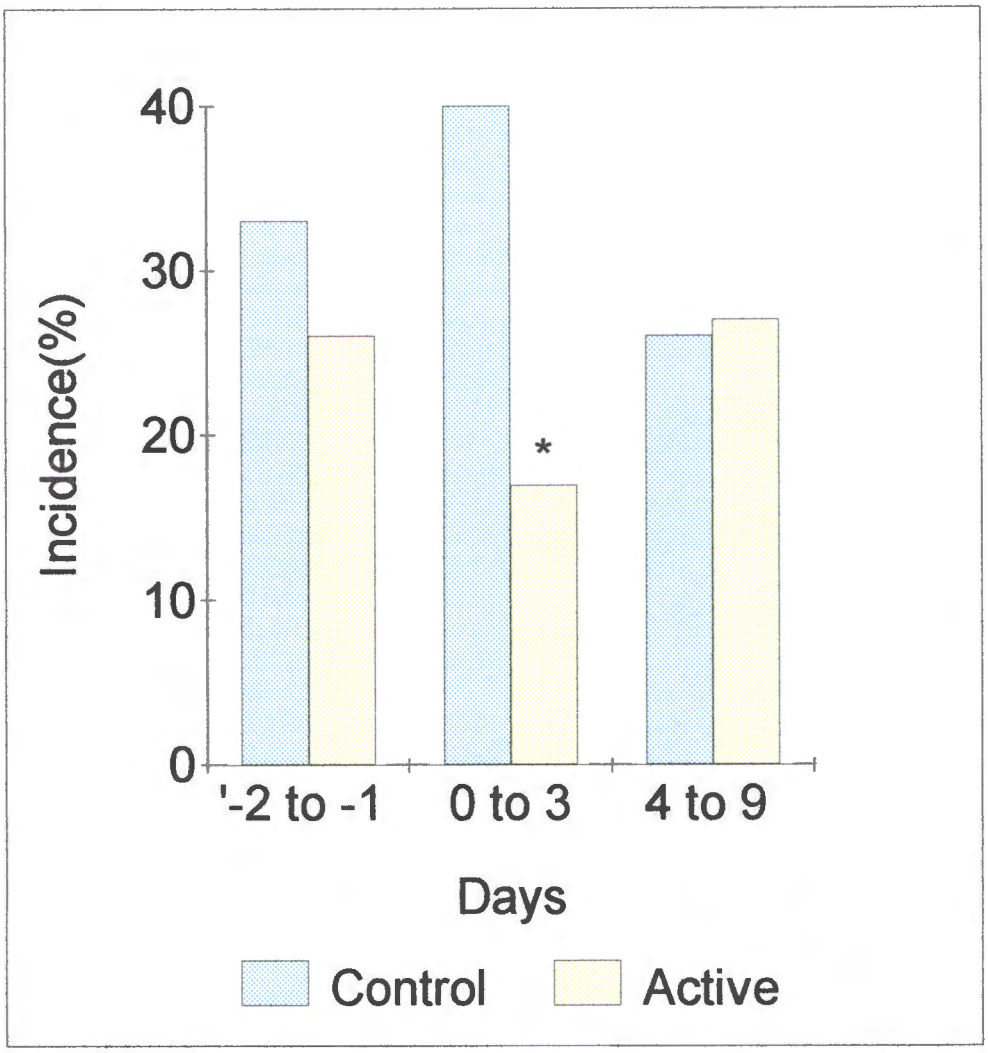

Figure 3.8: Incidence of all respiratory tract symptoms in ultradistance runners (n = 90). Significant difference between groups (* p = 0.028).

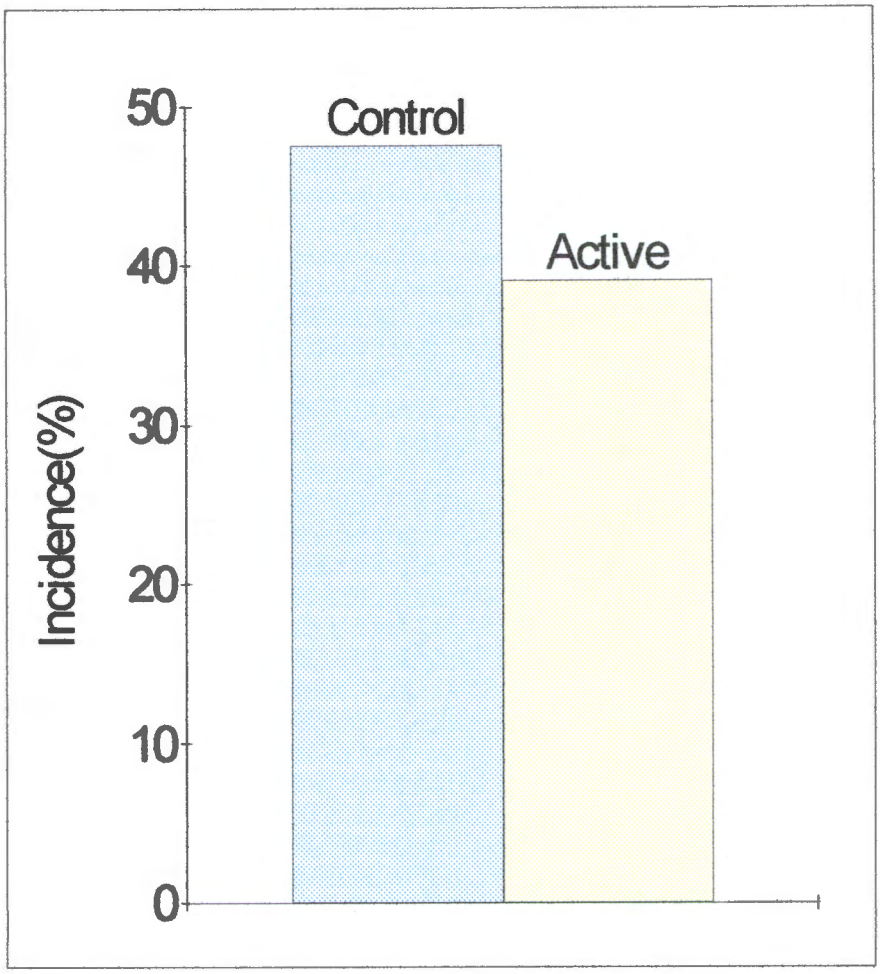

Figure 3.9: Incidence of all post race respiratory tract symptoms in ultradistance runners fron Day 0 to 9 (n = 90). No significant difference between groups.

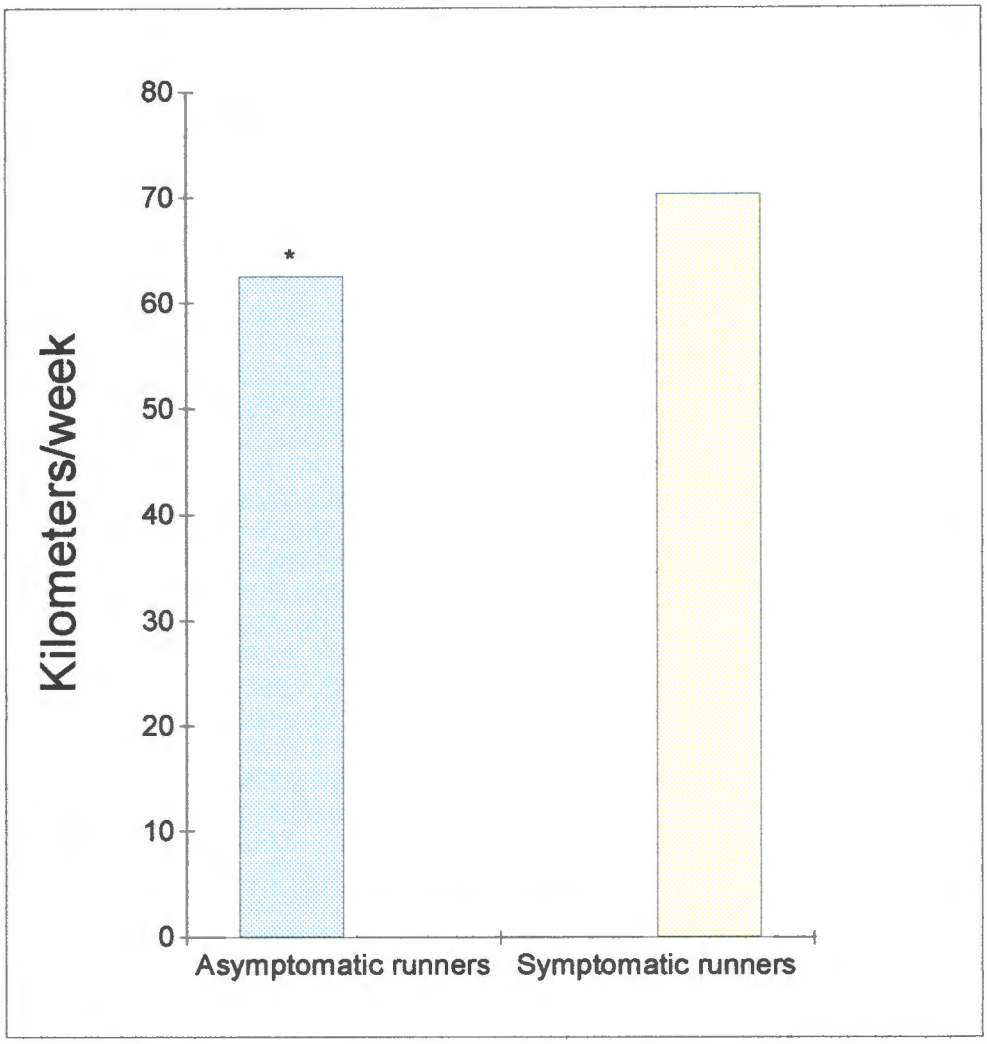

Figure 3.10: The training volume in asymptomatic runners (n = 48) and symptomatic runners (n = 48). Significant difference between groups (* p = 0.0156).

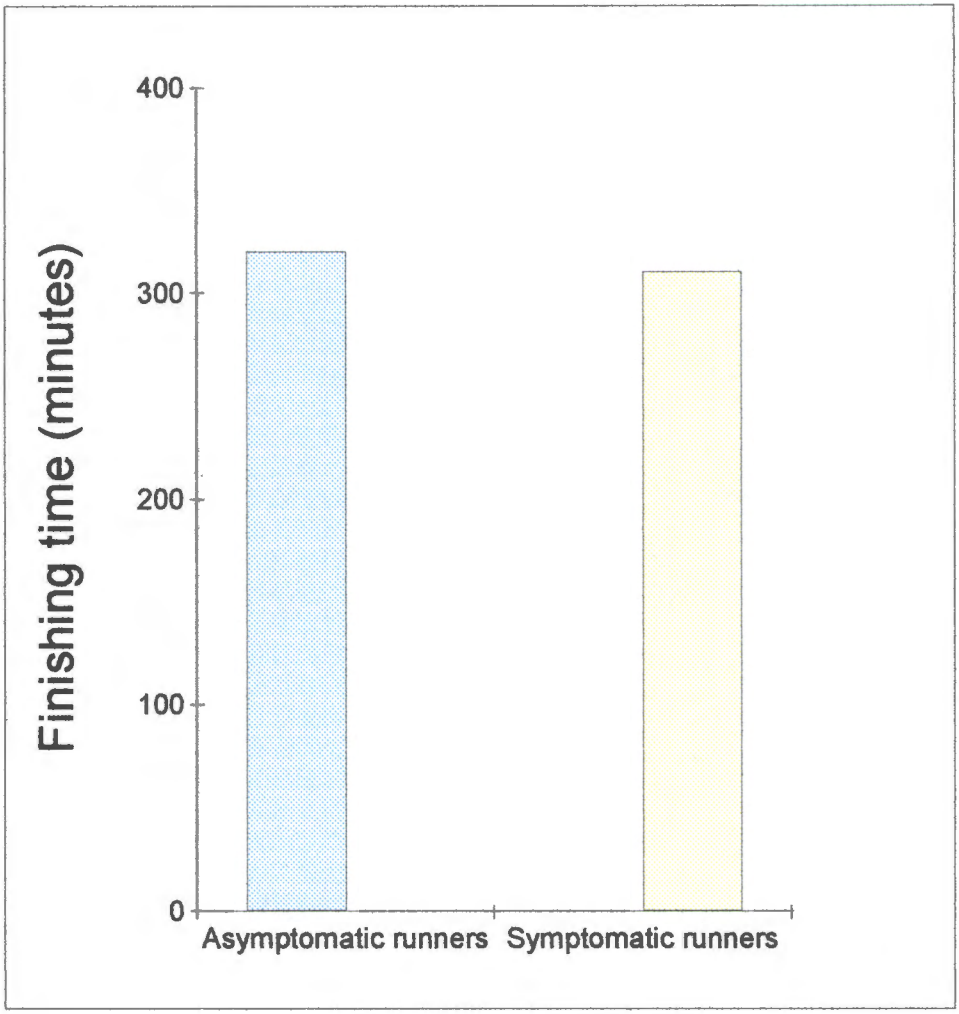

Figure 3.11:The finishing times in asymptomatic runners (n = 48) and symptomatic runners (n = 46). No significant differences between groups (p > 0.05).

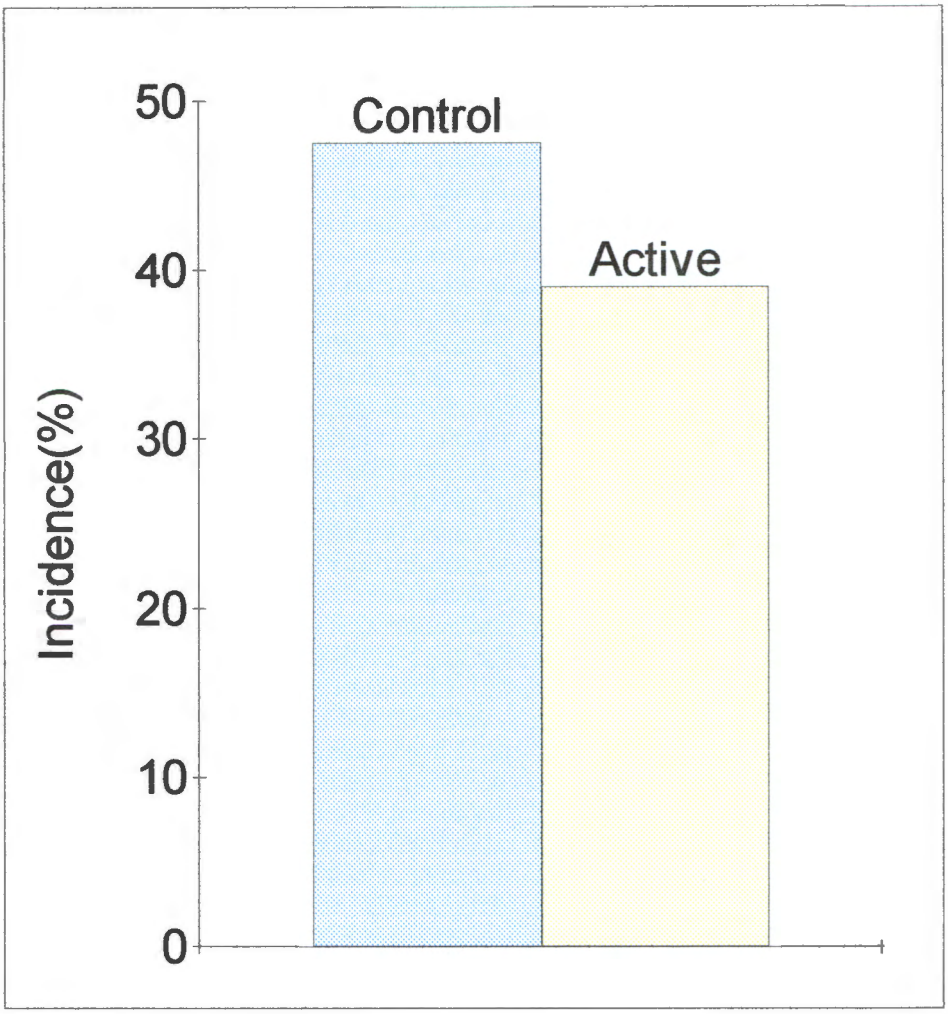

Figure 3.12: **Incidence of all post race upper respiratory tract symptoms in ultradistance runners from Day 0 to 9 (n = 90). No significant difference between groups.**

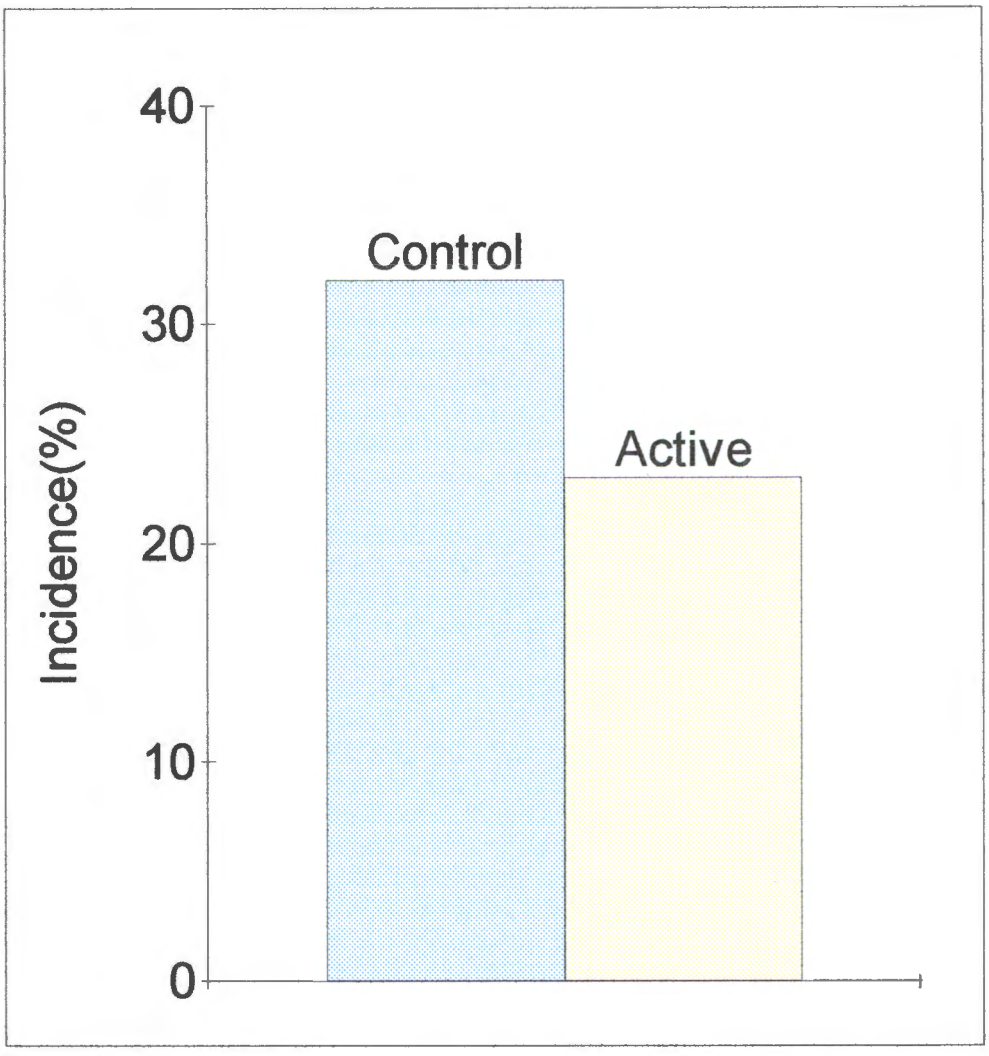

Figure 3.13: **Incidence of all post race nasal symptoms in ultradistance runners from Day 0 to 9 (n = 90). No significant difference between groups.**

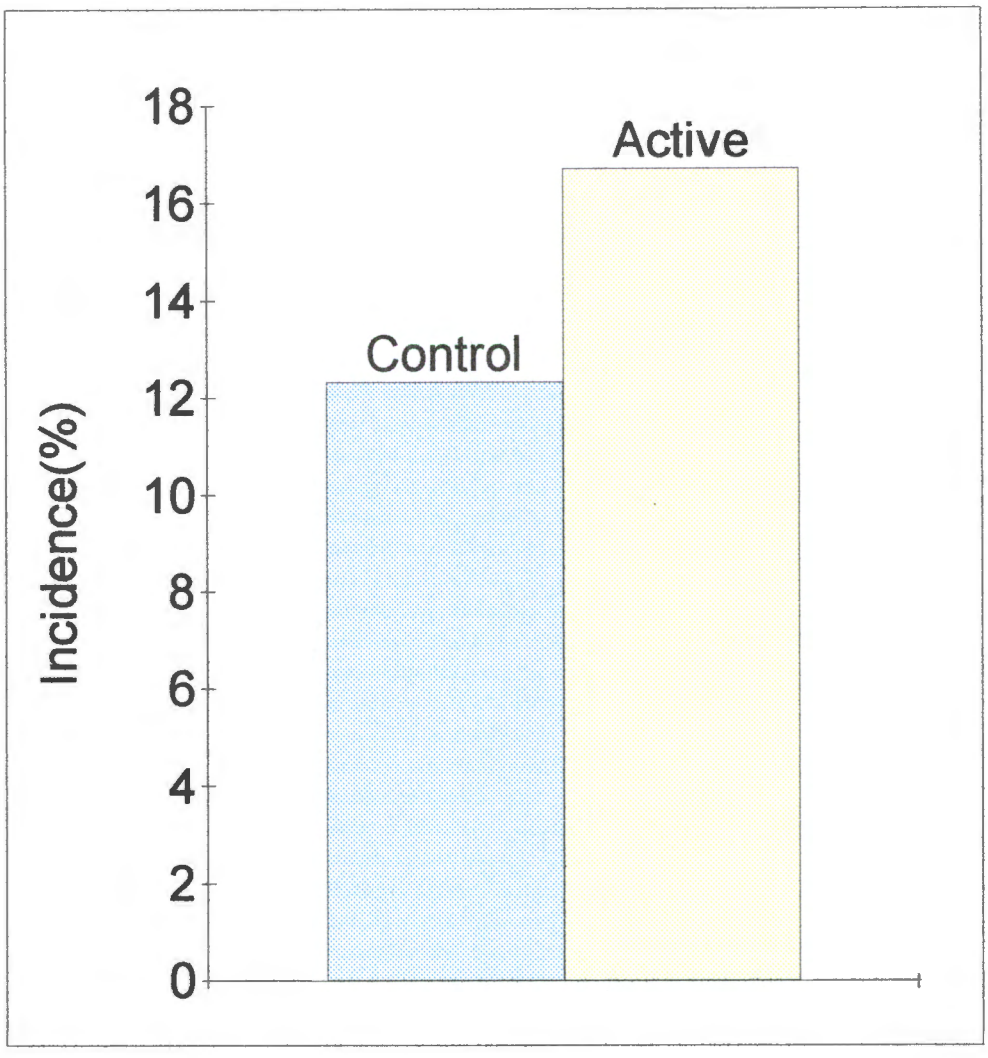

Figure 3.14: **Incidence of post race cough in ultradistance runners from Day 0 to 9 (n = 90). No significant difference between groups.**

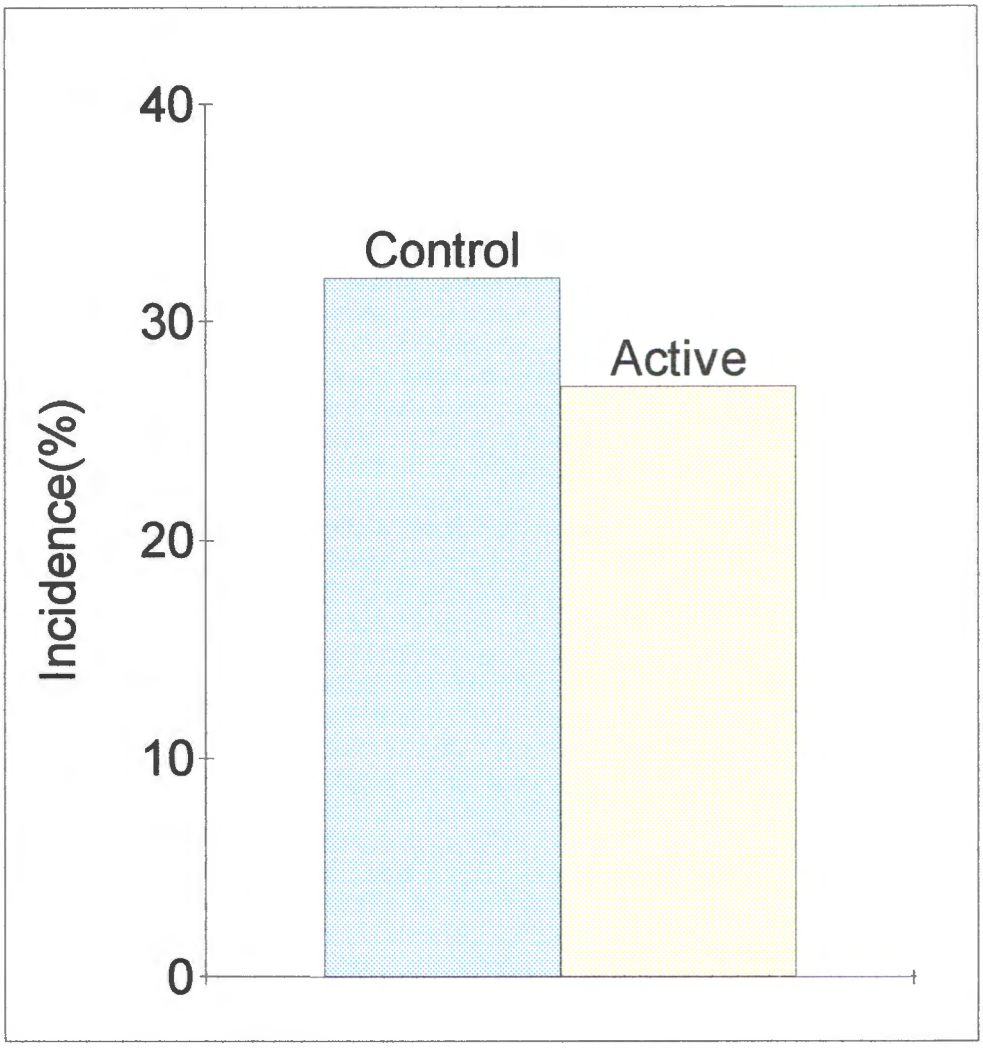

Figure 3.15: **Incidence of post race sore throat in ultradistance runners from Day 0 to 9 (n = 90).**
No significant difference between groups.

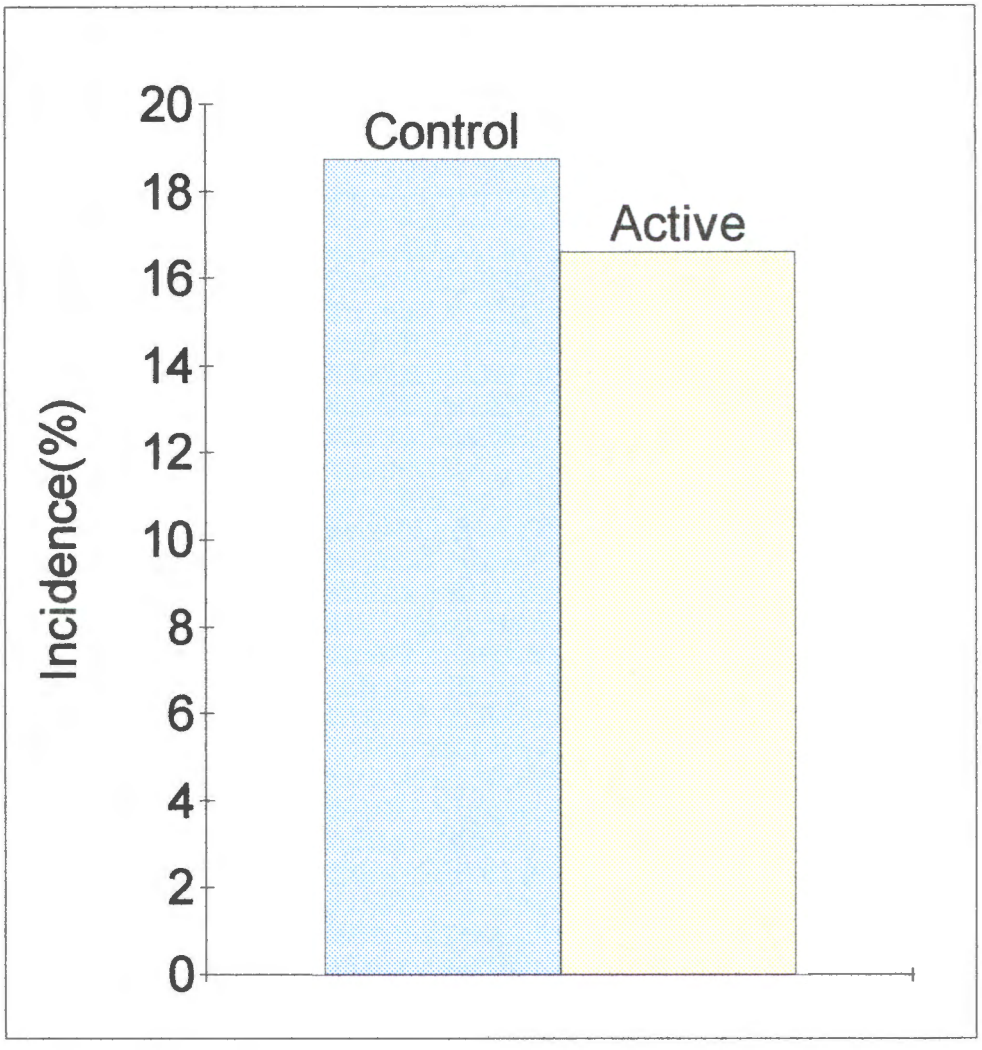

Figure 3.16: **Incidence of post race runny nose in ultradistance runners from Day 0 to 9 (n = 90).**
No significant difference between groups.

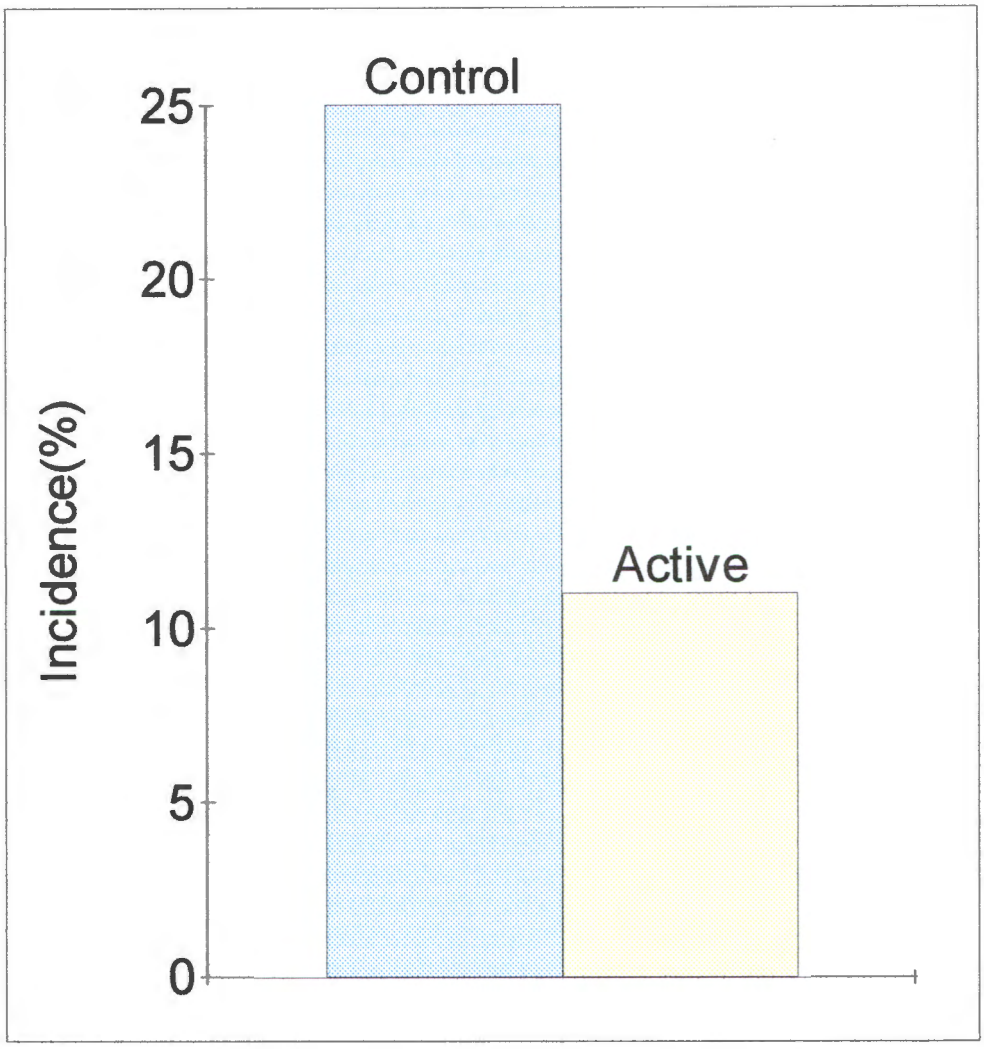

Figure 3.17: **Incidence of post race blocked nose in ultradistance runners from Day 0 to 9 (n = 90). No significant difference between groups.**

Chapter 4

Summary

Epidemiological data shows that athletes who engage in ultradistance running are at increased risk for developing symptoms of upper respiratory tract infection during times of intense training and the two week post-race period (Nieman et al, 1990; Peters, 1990; Peters et al, 1983; Peters et al, 1993; Peters et al, 1996). In contrast, athletes who engage in moderate physical activity report less symptoms and may show enhanced resistance to infection (Nieman, 1994; Nieman et al, 1993; Nieman et al, 1990). Although numerous immunological changes may be documented after intense or prolonged exercise, most are transient and their exact role in producing susceptibility to infection remains elusive (Simon, 1987).

Upper respiratory tract infections however, remain a real dilemma for athletes. Even a minor illness limits training and this may impair performance in an upcoming event. In addition, the dangers of exercising while infected with a virus are well known. As these infections are mainly viral, treatment is symptomatic and prevention would therefore be more desirable (Heath et al, 1992; Shephard et al, 1993).

One of the major limitations of most previous studies to determine the relationship between upper respiratory tract infection and exercise is that they relied on self reported symptoms by the athlete. A true measure of outcome is impossible to

ascertain without a clinical examination and laboratory documentation of infection.

In this study there was no evidence of viral or bacterial infection in any of the subjects who presented with symptoms, as documented by negative viral gargle cultures and bacterial cultures from throat swabs. In addition, the administration of a topical anti-inflammatory/anti-bacterial agent (fusafungine) effectively reduced the incidence of upper respiratory tract symptoms from 40% to 17% in the first few days after an ultradistance event. These findings imply that in many athletes the symptoms of upper respiratory tract infection that are reported may in fact be due to local inflammation and not actual infection. This has important implications for further participation in running as well as the necessity for treatment.

Further research should therefore be directed at documenting an increase in true infection in ultradistance runners as opposed to self reported symptoms. In addition, it may be useful to investigate the benefit of using a pure topical anti-inflammatory agent such as an inhaled local corticosteroid.

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APPENDIX 1

CASE REPORT FORM

Title :

The effect of fusafungine (Locabiotal ®) on the incidence of upper respiratory tract infections in ultra distance runners

Patient N° ☐ ☐ ☐

Patient Surname ☐

Patient Initials | | | | | | | | | **Patient Number** | | | | |

SECTION A - Pre Race Assessment

1. Personal Details

Surname :

First Names

Age :

Date of Birth : dd mm yy

Weight : kg

Height : cm

Occupation :

Work Tel N° : code

Home Tel N° : code

Postal Address :

2. General Medical History

A. Family History

Have any of your relatives ever had the following ? Please tick yes / no and list your relationship of that person to you

Description	yes	no	Relationship
High Blood Pressure			
Cancer			
Epilepsy			
Psychiatric Abnormalities			
Asthma			
Tuberculosis			
Diabetes			
Kidney Disease			

Patient Initials | | | | | | | | | **Patient Number** | | | | |

2. General Medical History

B. Personal Medical History

Have you had any of the following (please tick the appropriate block)

Description	yes	no	Description	yes	no
Surgery			Genetic Disorders		
Head Injury with unconsciousness			Sugar in urine		
Kidney stones			Epilepsy		
Ear, nose & throat disorders			Weakness / Paralysis		
Hay fever			Hernia		
Asthma			Disease of joints		
Tuberculosis			Lower back pain		
Rheumatic fever			Cancer		
Heart murmer			Allergy		
High blood pressure			Skeletal pain / cramps		
Chest pain at rest			Blood in the stool		
Chest pain during exercise			Stomach or intestinal disorder		
Recurrent diarrhoea			Jaundice or Hepatitis		
Urinary tract infection					

1. Do you smoke ? yes no

2. Approximately how many respiratory tract infections have you had on average over the past five (5) years (per year) ?

   none 1 2 3 4 > 5

3. How many hours per night do you sleep on average ? < 5 5-6 6-7 8-9 > 9

4. Do you live alone with friends family family & children

5. Have you had any extraordinary social / emotional stress recently ?

   (e.g. death / illness in family, marital disharmony, work related) ? yes no

6. How much alcohol do you drink (tots, glasses of wine / beers) per week 0 1-3 3-5 5-7 > 7

Patient Initials | | | | | | | | | **Patient Number** | | | | |

2. General Medical History

C. Training History

1 How many years have you participated in endurance running ? [< 1] [1-3] [4-6] [6-10] [>10]

2 In the last six (6) months during training, what has been :

i) Your km / week done on average [< 40] [40 - 60] [60 - 80] [> 80]

ii) Average speed in mins / km [> 5] [4 - 5] [3 - 4] [< 3]

4 During the last month has your training distance ? [remained the same] [increased] [decreased]

5 During the last month has your training intensity ? [remained the same] [increased] [decreased]

6 Do you participate in other sport ? [yes] [no]

D. Nutritional and Supplements

1 Are you taking dietary supplements / vitamins ? : [yes] [no]

2 What is its / their name (s) : _____

_____

3 What dosage are you taking (of each if applicable) ? : _____

_____

4 For how long have you been taking it / them ? : _____

5 Do you carbo - load before the race : [yes] [no]

Patient Initials | | | | | | | | | **Patient Number** | | | | |

SECTION A - Pre Race Assessment

2. General Medical History

E. Physical Examination

Pulse rate (beats / min)	< 60	60 - 70	70 - 80	> 80
Temperature	36,6	37 - 38	38 - 39	> 40

Description	yes	no	Specify
Lymph nodes in neck			
Pharynx inflamed			
Nasal Mucosa inflamed			
Ear drums inflamed			
Left lung apex clear			
Left lung base clear			
Right lung apex clear			
Right lung base clear			
Heart sounds normal			
Heart murmers			

Included in Trial	Yes	No
Instructed on use of Locabiotal	Yes	No
Locabiotal dispensed	Yes	No
Patient diary A given	Yes	No

Patient Initials | | | | | | | | | **Patient Number** | | | | |

SECTION B - Day 6 Assessment

Day 6 Assessment

1. Patient Diary A received : yes | no

2. Symptoms of URTI present : yes | no

3. If symptoms present - physical examination

   a. Pulse rate (beats / min) : < 60 | 60 - 70 | 70 - 80 | > 80

   b. Temperature : 36,6 | 37 - 38 | 38 - 39 | > 40

Description	yes	no	Specify
Lymph nodes in neck			
Pharynx inflamed			
Ear drums inflamed			
Ear drums inflamed			
Left lung apex clear			
Left lung base clear			
Right lung apex clear			
Right lung base clear			
Heart sounds normal			
Heart murmers			
Throat swabs done for bacterial culture			
Cargle done for viral culture			
Throat swab positive			
Gargle positive			

Patient Initials | | | | | | | | | **Patient Number** | | | | |

SECTION C - Day 12 Assessment

Day 12 Assessment

1. Patient Diary B received : yes | no

2. Symptoms of URTI present : yes | no

3. If symptoms present - physical examination

a. Pulse rate (beats / min) : < 60 | 60 - 70 | 70 - 80 | > 80

b. Temperature : 36,6 | 37 - 38 | 38 - 39 | > 40

Description	yes	no	Specify
Lymph nodes in neck			
Pharynx inflamed			
Ear drums inflamed			
Left lung apex clear			
Left lung base clear			
Right lung apex clear			
Right lung base clear			
Heart sounds normal			
Heart murmers			
Throat swabs done for bacterial culture			
Cargle done for viral culture			
Throat swab positive			
Gargle positive			

Patient Initials | | | | | | | | | **Patient Number** | | | | |

PATIENT DIARY A

1. What was your time for the race _____ hours _____ minutes

2. Development of symptoms

Please tick the appropriate block indicating the day of onset and days of duration of any symptoms experienced

Description	Thu 4.4.96	Fri 5.4.96	Sat 6.4.96	Sun 7.4.96	Mon 8.4.96	Tue 9.4.96
Sore throat						
Blocked nose						
Running nose						
Cough						
Fever						
General body aches						
Tiredness / fatigue						
No symptoms						

3. Locabiotal administration Chart

Day & Date	Morning	Lunchtime	Afternoon	Evening
Thursday 4.4.96				
Friday 5.4.96				
Saturday 6.4.96				
Sunday 7.4.96				
Monday 8.4.96				
Tuesday 9.4.96				

Please be honest - leave out any dosage not taken

4. Did you experience any side effect from the Locabiotal ? yes no

Specify : _____

Patient Initials | | | | | | | | | **Patient Number** | | | | |

PATIENT DIARY B

1. Development of Symptoms

Please tick the appropriate block indicating the day of onset and days of duration of any symptoms experienced

Description	Thu 10.4.96	Fri 11.4.96	Sat 12.4.96	Sun 13.4.96	Mon 14.4.96	Tue 15.4.96
Sore throat						
Blocked nose						
Running nose						
Cough						
Fever						
General body aches						
Tiredness / fatigue						
No symptoms						

3. Locabiotal administration Chart

Day & Date	Morning	Lunchtime	Afternoon	Evening
Thursday 10.4.96				
Friday 11.4.96		II		
Saturday 12.4.96				
Sunday 13.4.96				
Monday 14.4.96				
Tuesday 15.4.96				

Please be honest - leave out any dosage not taken

4. Did you experience any side effect from the Locabiotal ? yes no

Specify :

APPENDIX 3

APRIL 1996

DIETARY ANALYSIS
PRELIMINARY DATA FOR DR M. KIESSIG - SPORTS SCIENCE INSTITUTE OF S.A.

NAME: DATE:
AGE: WEIGHT: HEIGHT:
TRAINING LOAD: daily weekly

In order to obtain useful and accurate dietary information for the purpose of this study, please record all the foods you eat over a 3 day period ***as you eat them!*** It is very important that you try and document the ***quantities*** of ***each*** food item or drink in the dish or meal. Where possible please use standard serve sizes such as cups, tablespoons, teaspoons etc. For meat and other protein products describe the cooked piece(s) in terms of number of matchboxes or actual weight.

DAY 1

	FOODS EATEN	QUANTITY	PREPARATION/ ADDITIONS/ SAUCE
Morning	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Mid-morning	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Lunch	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Mid-afternoon	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Evening	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Late-evening	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		

WHAT NUTRITIONAL SUPPLEMENTS DID YOU TAKE TODAY?

DAY 2

	FOODS EATEN	QUANTITY	PREPARATION/ ADDITIONS/ SAUCE
Morning	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Mid-morning	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Lunch	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Mid-afternoon	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Evening	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Late-evening	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		

WHAT NUTRITIONAL SUPPLEMENTS DID YOU TAKE TODAY?

DAY 3

	FOODS EATEN	QUANTITY	PREPARATION/ ADDITIONS/ SAUCE
Morning	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Mid-morning	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Lunch	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Mid-afternoon	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Evening	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		
Late-evening	beverage fruit/veg bread/cereal milk/yoghurt butter/marg/oil *protein		

WHAT NUTRITIONAL SUPPLEMENTS DID YOU TAKE TODAY?
WHAT ADDITIONAL SUPPLEMENTS ARE YOU TAKING?